



CALIFORNIA INSTITUTE FOR
CIRM
REGENERATIVE MEDICINE

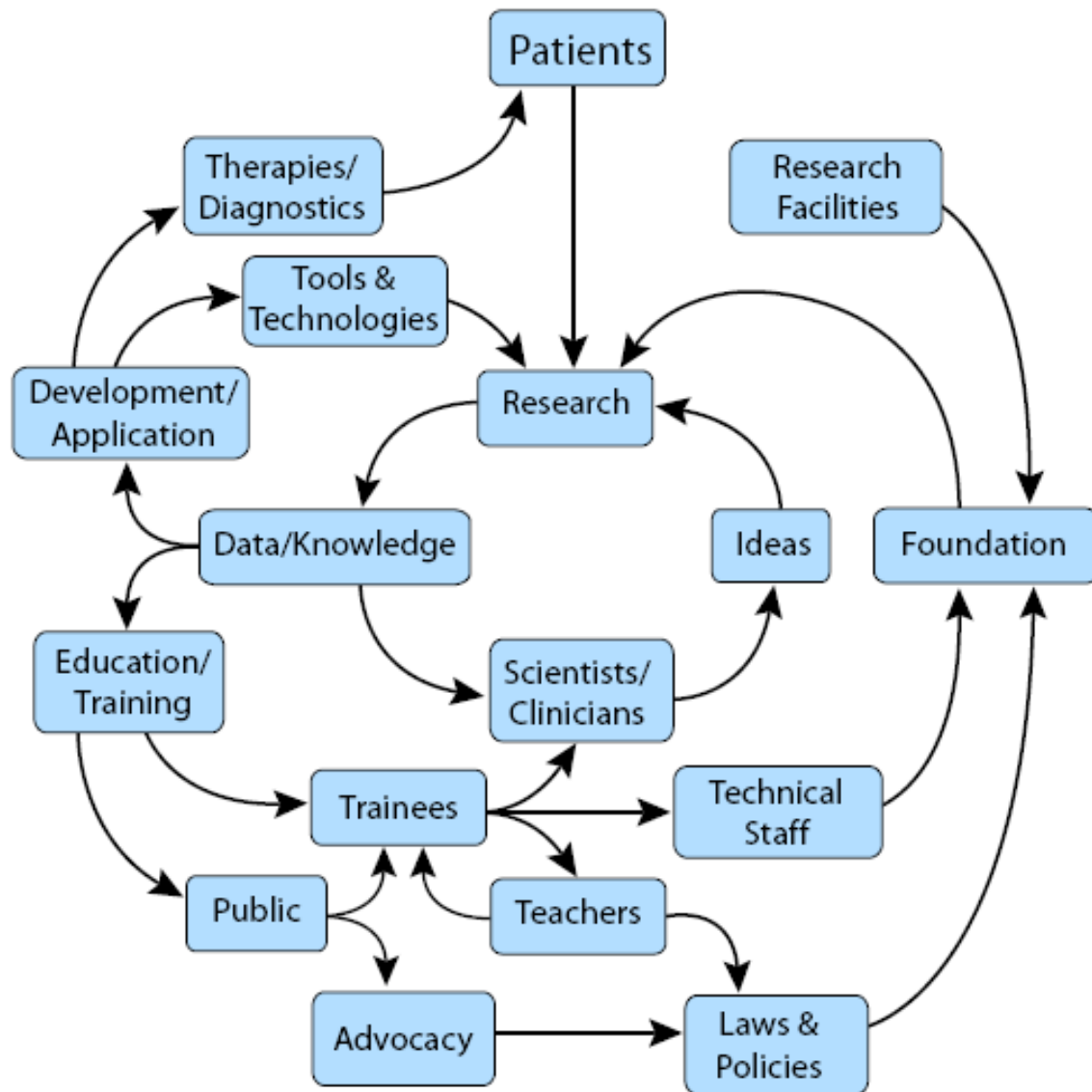


**Turning stem cells
into cures**

-Roman Reed

DRAFT

**Scientific Strategic Plan
October 2006**



The California Institute for Regenerative Medicine would like to thank the many contributors whose input was invaluable in developing this Scientific Strategic Plan, including Mr. Roman Reed, who coined the slogan that appears on the front cover.

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Chair's and President's Messages

To be written after the October 10 and 11, 2006 ICOC meetings.

Executive Summary

Introduction

The California Institute for Regenerative Medicine (CIRM) is a state agency created by Proposition 71, the California Research and Cures Bond Act of 2004. The Act authorizes the CIRM to use \$3 billion of General Obligation bonds to fund pioneering stem cell and other scientific research in the state. To guide CIRM in the use of these funds, the Independent Citizens Oversight Committee (ICOC) is to develop a Scientific Strategic Plan that defines the long-term objectives that CIRM will pursue and outlines a ten year program for achieving these objectives. During the ten year period, the Plan will be periodically reviewed to assess progress toward its goals and modified to address new opportunities and challenges.

***"Against all odds, we shall
succeed. We have a moral
obligation to every patient,
to every family, to every
Californian - to every
American - to succeed; and
so we shall."
-Robert Klein,
ICOC Chair***

Overview of the Planning Process

At its December, 2005 meeting, the ICOC charged the President and staff of CIRM with developing a draft of the Scientific Strategic Plan to be presented at the October 2006 ICOC meeting, with final approval of the plan in December 2006. The President proposed "A Plan for a Plan" that involved three stages: data gathering, data analysis and plan preparation. The data-gathering phase began with a scientific meeting held on October 1-2, 2005, entitled "Stem Cell Research: Charting New Directions for California". An international group of stem cell scientists addressed the question of developing scientific priorities for CIRM. Data-gathering continued through interviews with over 70 leading scientists, clinicians, patient advocates and others; through three scientific conferences on specific topics for the ICOC and the public; and through two focus meetings. CIRM staff then analyzed and organized the information that was gathered and drafted the plan.

Key to the development of the plan were two ICOC meetings in which a mission statement, values and strategic principles for the plan were developed. Throughout the process of plan development, a Strategic Plan Advisory Committee discussed strategic questions and advised the President and staff in plan development.

Opportunities and Challenges

The Scientific Strategic Plan recognizes that CIRM's ability to advance its mission will be influenced by both internal and external factors:

Internal Opportunities

- CIRM can implement new and innovative funding structures.
- CIRM is free to investigate all aspects of stem cell science.
- CIRM has substantial resources and a stable source of funding.
- CIRM has a highly focused mandate that will allow it to adopt administrative structures and procedures that are specific for stem cell research.

Internal Challenges

- CIRM has restrictions imposed by Proposition 71.
- CIRM has a finite amount of funding and a currently limited lifespan.

"Curing a disease like Type 1 diabetes, doing embryonic stem cell research, or doing cell therapy is not rocket science; it's a lot harder."

- Allen Spiegel,

***Albert Einstein College
of Medicine***

External Opportunities

- CIRM can become a leader in stem cell research.
- CIRM can help define the research and regulatory standards that will shape the development of stem cell-therapies in the US.
- CIRM can contribute to defining and exploring ethical issues in stem cell research.
- CIRM can benefit from, and contribute to, the rich research assets of California.
- CIRM can bridge gaps between people, such as those between basic researchers and clinicians and between academia and industry.
- CIRM can contribute to the development of the stem cell sector of the biotechnology industry in California.
- CIRM can create new, innovative models for public-private partnerships.

External Challenges

- CIRM must operate independently of federal funding institutions.
- CIRM operates in a field that is evolving and dynamic.
- CIRM will have an ever-increasing level of competition world-wide.
- CIRM must manage complex intellectual property issues.
- CIRM faces high expectations for therapeutic results.

Mission, Values and Strategic Principles

Mission

In accordance with the mandate of the citizens of California, as specified in the California Stem Cell Research and Cures Act, the mission of the California Institute for Regenerative Medicine is:

To support and advance stem cell research and regenerative medicine under the highest ethical and medical standards for the discovery and development of cures, therapies, diagnostics and research technologies to relieve human suffering from chronic disease and injury.

Values

The values that will guide and imbue our efforts and activities are as follows:

- Accountability
- Adaptability
- Collaboration
- Diversity
- Excellence
- Innovation
- Integrity
- Service
- Urgency

Strategic Principles

CIRM has also defined a series of strategic principles which will serve as the foundation for all its activities and which will form the backbone of future initiatives:

- Seeding Research
- Enabling Research
- Leveraging Resources
- Diversifying Risk
- Targeting Critical Gaps
- Focusing on Translational Medicine
- Using Comparative Advantage
- Supporting Goal Driven / Directed Science
- Setting Ambitious Goals
- Achieving Milestones
- Sharing Data
- Capturing Knowledge for Clinical Use
- Building Partnerships between Academia and Industry
- Fostering Dynamism

Strategic Objectives: Aspirations and Commitments

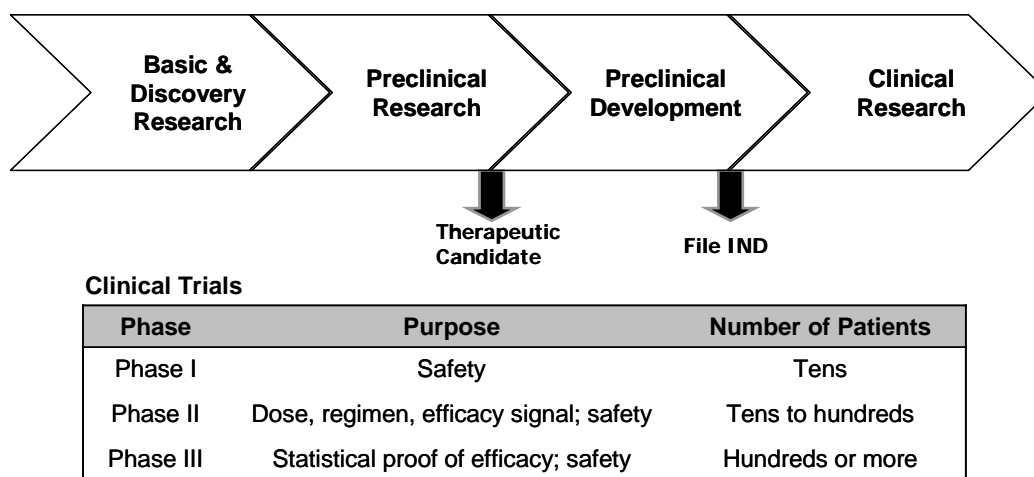
The Scientific Strategic Plan defines both *aspirational* goals that express our most ambitious hopes and *commitment* goals that are our realistic expectations of what we can achieve, given reasonable good fortune. It is the latter that should be used to judge our success in ten years.

The principle aspirational goal for CIRM is simple: to use stem cells to cure a variety of diseases. Although the challenges for meeting this goal are many, this is the goal that drives our efforts and our activities. A second aspiration is to make California the world-wide leader in stem cell research and the global center for stem cell research in the biotechnology and pharmaceutical industries.

CIRM's commitment goals are our covenant with the people of California for what we will accomplish over the next ten years to make the promise of stem cell therapy a reality. Given the time (8-10 years) and expense (\$800 million) of development for small molecule therapeutics, it is unlikely that CIRM will be able to fully develop stem cell therapy for routine clinical use during the ten years of the plan. Within that time span, however, we will be able to advance therapies for several diseases to early stage clinical trials, and to have therapies for other diseases in the pipeline. To provide a framework for our ten year goals, we provide a plausible model for the development of a cell therapy, based on the development of small molecule therapeutics:

Cell Therapy Development

Stages of Cell Therapy Development



In our model, development is described as occurring in four discrete stages:

- *Basic and discovery research*, which provides the foundation for therapy development.
- *Preclinical research*, where strategies for disease treatment are explored.

- *Preclinical development*, where the studies necessary to meet the Food and Drug Administration (FDA) regulatory requirements for an Investigational New Drug (IND) application prior to testing in humans are conducted.
- *Clinical research*, where the efficacy and safety of a treatment is tested in humans.

Ten Year Goals

The goal of CIRM at ten years will be to have some therapies in clinical development, with others in the pipeline. Our goals for fundamental and preclinical research at ten years will be the basis for the continuous development of therapies beyond the endpoint of the plan. With these considerations in mind, CIRM commits to the following 10 year goals:

"Failure is an inevitable part of success."
- Joan Samuelson,
ICOC Member

- Goal I: CIRM grantees will have clinical proof of principle that transplanted cells derived from pluripotent cells can be used to restore function for at least one disease.
- Goal II: CIRM grantees will have therapies based on stem cell research in Phase I or Phase II clinical trials for 2-4 additional diseases.
- Goal III: CIRM grantees will achieve a level of success that will attract private capital for funding further clinical development of stem cell therapies.
- Goal IV: CIRM will have funded new approaches for achieving immune tolerance for transplantation that are in pre-clinical development.
- Goal V: Using stem cell research, CIRM funded investigators will have established proof of principle in preclinical animal models for treatment of 6-8 diseases.
- Goal VI: CIRM funded investigators will have created disease-specific cell lines for 20-30 diseases and used them to gain new information about pathogenesis, to identify new drug targets and to discover new therapeutics.
- Goal VII: CIRM will have enabled development of new procedures for the production of a variety of stem and / or progenitor cells that meet GMP requirements.
- Goal VIII: Through research sponsored by CIRM and others, a thorough description of the steps of differentiation leading to the production of the various cells of the body will be achieved.
- Goal IX: Through research sponsored by CIRM and others, the factors regulating the self-renewal and oncogenic potential of embryonic stem cells and their derivatives will be identified and characterized.
- Goal X: CIRM will have enabled development of new methods for tissue replacement based on stem cell research.

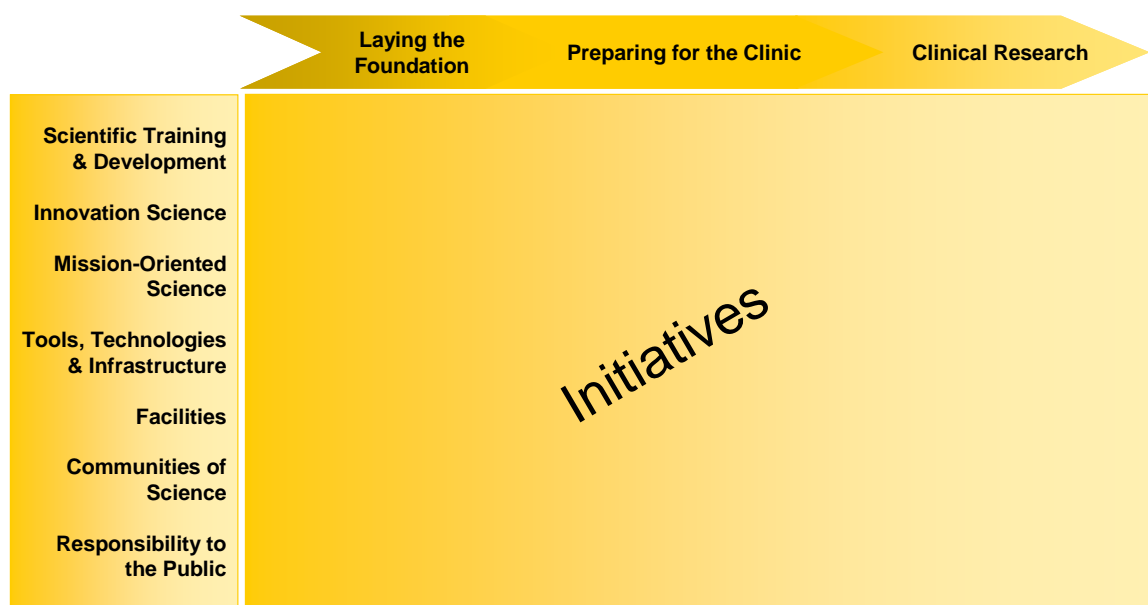
Five Year Goals

These goals will be used as milestones to gauge progress toward the ten year goals

- Goal I: CIRM grantees will have six therapies based on stem cell research in pre-clinical development.
- Goal II: CIRM grantees will have developed new methods of making stem cell lines.
- Goal III: CIRM grantees will have successfully created disease-specific stem cell lines for four diseases.
- Goal IV: CIRM grantees will have developed methods of growing stem cells in defined media.
- Goal V: CIRM will have enabled establishment of a stem cell bank.
- Goal VI: CIRM funded investigators will have demonstrated methods for inducing immune tolerance in animal models.
- Goal VII: CIRM will have increased the workforce of stem cell researchers in California.
- Goal VIII: CIRM grantees will have established tools for toxicity testing based on stem cell research.
- Goal IX: CIRM will have established effective partnerships in stem cell research between scientific teams in non-profit and commercial sectors.
- Goal X: CIRM will have established national and international collaborations in stem cell research.

The Strategic Planning Framework

CIRM will achieve its strategic objectives through a series of initiatives that, taken together, will define the CIRM research program. To place these initiatives within a strategic framework we define a “space”, using two coordinate systems, one related to progress from the laboratory bench to the clinic and the other representing the resources that will be deployed:



Charting the Path to Therapies

Laying the Foundation

There is general agreement that before human embryonic stem cells (hESCs) can be developed for widespread clinical use, much work on their fundamental biology must be done. Many of the questions that CIRM will attempt to explore are outlined in this section.

An early challenge is to understand what defines an embryonic stem cell and how different hESC lines differ from each other and from non-embryonic stem cells. Our understanding of both of the two characteristic features of embryonic stem cells, their capacity for self-renewal and their ability to produce a wide variety of specialized cells, is incomplete.

If stem cells are to be used as therapies, it will be important to have available a large number of stem cell lines of diverse genetic backgrounds that represent the range of human populations and to understand the influence of these backgrounds on their properties. In particular, the availability of embryonic stem cell lines with genetic mutations that lead to disease will be a powerful tool for understanding the cellular basis of pathogenesis for many disorders and for drug discovery.

In the body, stem cells occupy special locations, or niches, whose components interact with stem cells to regulate cell division and to influence differentiation. Understanding the role of the niche is important in guiding in vitro attempts to regulate stem cells; it is also important to understand the behavior of endogenous stem cells, which may be mobilized for combat disease and injury.

Preparing for the Clinic

Pre-clinical research and development involves the identification of a potential therapeutic for a particular disease, demonstration of proof-of-principle in a cellular or animal disease model and preparation of the therapeutic for use on humans. The latter is particularly important and often not appreciated. Before approval can be obtained from the FDA for an Investigational New Drug (IND) for testing in humans, a therapeutic agent must be shown to be safe and effective in non-human models. The quality of a therapeutic agent must be assessed, including demonstrations of its purity and its ability to be reproducibly produced. An early challenge for pre-clinical development of stem cell therapies will be to develop methods for production of the cells in GMP facilities.

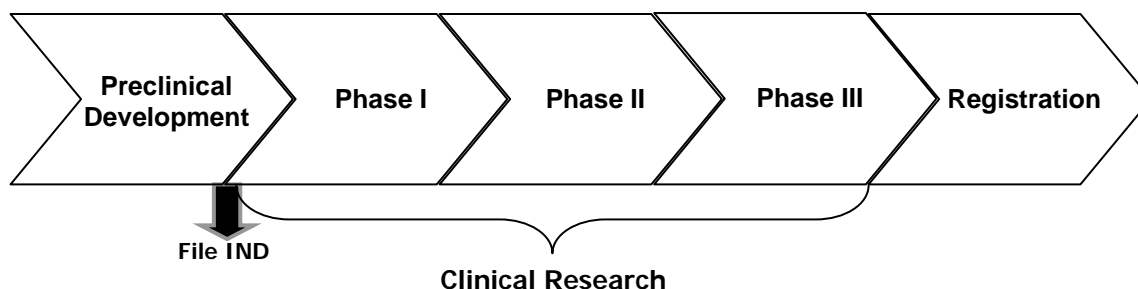
To bring stem cell therapy to widespread use in the clinic, the problem of immune rejection must be addressed. Currently, for allogeneic transplants, immune suppression is required to prevent rejection of the tissue by the recipients, leading to unwanted or life-threatening complications. For some indications, patient-based stem cell lines offer a potential solution, but the current

expense and difficulty of creating a tailor-made cell line makes this solution unlikely to be practicable on a large scale. Another more general solution is to replace the immune system to make it compatible with the transplanted cells; other strategies may also be possible. Other technological needs for development include new methods of introducing cells; the creation of artificial niches to contain transplanted cells; and automated methods of growing cells.

Pre-clinical development, which is in general not funded by the federal government, occurs largely in pharmaceutical firms and biotechnology companies. In large, well-capitalized companies, pre-clinical development can be easily financed, but in small companies, the ability to carry out pre-clinical development for a promising treatment is often the difference between success and failure. If CIRM is to be successful in bringing therapies to the clinic that are based on stem cell research, we will need to develop new funding mechanisms to address the problems posed by pre-clinical development.

Clinical Research

Ultimately, any potential stem cell or stem cell derived cure or therapy must be rigorously tested in human subjects before it can be made broadly available to patients. Clinical trials are designed and conducted to address safety, dose, delivery, mechanism, regimen, and efficacy with the ultimate goal of developing a cure or therapy that can benefit patients. They are conducted in three sequential phases: Phases I, II and III. Each phase builds on the information gathered in the previous phase and is designed to generate additional information about the candidate therapy.



Phase	Outcomes	Numbers of Patients	Phase Duration (Years)
Phase I	Safety, dose, regimen, mechanism	Tens	1 - 2
Phase II	Dose, regimen, mechanism, efficacy signal; safety	Tens to hundreds	1 - 5
Phase III	Statistical proof of efficacy; safety	Hundreds or more	2 - 5

Because of their expense and because of the time required to reach this stage of clinical development, CIRM is unlikely to fund Phase III trials over the ten year time span of the Strategic Plan. Although CIRM will fund some Phase II trials, most funded studies will be Phase I trials. Some of these I trials will be conducted by investigative groups at academic medical centers (AMCs); others may be conducted by private companies, often in partnership with AMCs.

Clinical research is heavily regulated by the FDA in the U.S. The FDA requires that a therapeutic candidate to be tested in humans be produced by well defined, documented, reproducible procedures that result in lot-to-lot consistency of a product that meets standards of purity, identity and potency and that there be a reasonable expectation of safety and benefit based on preclinical studies. Because the field is new and will be developing rapidly, FDA regulations may be expected to evolve. By maintaining communication with the FDA, CIRM and CIRM-funded investigators can play an important role in aiding the emerging development of the standards.

Because it involves human subjects, clinical research is arguably the most difficult form of biological research. Subjects must freely and voluntarily consent to the trial; every precaution must be taken to minimize risk to the subject; and there must be the prospect of potential benefit. To maintain these standards, clinical research is necessarily complex, particularly when it has the intent to register a therapeutic candidate for marketing approval.

Developing and Enabling Critical Resources

Scientific Training and Development

There is a critical need for trained personnel in human embryonic stem cell research at all levels. The restrictions on federal funds have severely limited the number of laboratories and laboratory personnel working on human embryonic stem cells. The scarcity of funds has particularly discouraged new investigators who are beginning their independent careers. The research planned by CIRM will require a large expansion in the number of trained scientists in this field. Basic, translational, and clinical scientists trained in stem cell science are all in short supply. Trained technical staff will also be needed. It will thus be important for CIRM to sponsor training programs in stem cell research at both the professional and technical levels.

Innovation Science

An important part of CIRM's program, especially in the early years, will be to encourage investigator-initiated, curiosity-driven science relevant to the development of stem cell therapies. Although much of CIRM's research program will be shaped by initiatives with specific goals, the free inflow of new ideas must be maintained. To fully exploit the creative energies of California scientists, we will need to have broad initiatives that will allow scientists to obtain funding to explore new ideas or new techniques that we cannot now know or predict. Limited federal

support for innovation science on stem cells makes it imperative that CIRM support open-ended, investigator-driven research related to stem cells.

Mission-Directed Science

Although scientific understanding provides the foundation, the main thrust of CIRM's research is to develop therapies. Thus, a substantial body of CIRM research will support research projects directed toward specific ends. CIRM will deploy both grants and contracts in the support of such mission-directed science. The specific aims to be achieved will be identified through consultation with the scientific community by a variety of mechanisms.

CIRM Special Program Initiatives

CIRM Special Program Initiatives are those in which the Institute proposes to organize funding in new and unconventional ways in order to promote progress. The hallmarks of the first initiatives in the program will be an emphasis on:

- Collaborative teams
- Specific goals with a timeline and milestones
- Active management of the project
- Active CIRM participation in evaluation and project management

Teams will be organized to attain specific goals within a given time and the project will be actively managed. Progress will be evaluated and strategy modified as necessary by an advisory group that includes members of the team, outside scientists, and CIRM personnel.

Tools / Technologies and Infrastructure

Many of CIRM initiatives will be directed toward projects to develop specific tools, enabling technologies, or infrastructures that will support the basic, translational and clinical science needed to develop therapies. CIRM may also wish to set up one or more specialized centers that will develop technology and make it widely available for the broader community. One example that has been widely discussed is a stem cell bank that would maintain, store and characterize stem cells lines developed in California and elsewhere. Finally, CIRM may wish to provide infrastructure that will help investigators through consultation, service or training, such as to help academic investigators navigate the requirements necessary to obtain a license for an Investigational New Drug (IND).

Facilities

An essential component to achieve the goals of CIRM will be adequate research space for human embryonic stem cell research. This need has two sources. First, as new stem cell investigators are recruited to non-profit institutions in California and as new investigators are

trained, new facilities will be required to house them. Second, in many cases, space for research on human embryonic stem cells will need to be separated from space used to carry out NIH-funded research. There is thus an immediate need for space dedicated to human embryonic stem cell research in which cell lines that fall outside the federal guidelines can be used. CIRM may use up to 10% of its funds, as specified in Proposition 71, to build, renovate and equip both large- and small-scale facilities for human embryonic stem cell research.

Communities of Science

CIRM will engage in a variety of activities to create a vigorous, energetic and committed scientific community of stem cell research in California, including researchers in both non-profit research institutions and in the commercial sector. In addition to supporting and encouraging scientific relationships within the state, CIRM will need to help develop and facilitate scientific cooperation between California scientists and those in other parts of the United States and abroad. These partnerships may be particularly useful in leveraging CIRM-funded research.

Responsibility to the Public

Scientific research always takes place in a cultural context; this is especially true for stem cell research. CIRM funds research with a strong mandate from the California public; accordingly, we have a responsibility to explore the impact of stem cell research on the California public as well as to convey an accurate and unbiased account of the discoveries and potential medical benefits that arise. CIRM also has a responsibility to fund scholarly research on ethical and legal matters related to stem cell research and research on the social, economic and health-related impact of that research on society. In addition, CIRM should have an active program of education and communication directed to the general public.

For complex reasons, the diversity of California is not adequately reflected in the scientific community and CIRM will need to make special efforts to encourage the training and education of minority scientists. CIRM will also need to ensure that clinical trials of therapies resulting from stem cell research include minority populations. Finally, CIRM will make special efforts to maintain communication with its diverse public constituency.

In addition to our responsibility to the general public, CIRM has a special responsibility to patients and patient advocacy groups. They define our purpose and reason for being and it is important that we maintain strong lines of communication with them, both through our communications activities and as we continue to refine and develop our research program.

Initiatives to Address Needs and Aims

To support its mission and achieve its objectives, CIRM will launch a series of scientific initiatives. These initiatives, which are organized according to the categories defined in the

"Developing and Enabling Critical Resources" section of the Scientific Strategic Plan, are discussed in detail in the following pages. The following table outlines these initiatives and indicates which of the three broad categories defined in the "Charting the Path to Therapies" section of the plan they support:

Initiative	Laying the Foundation	Preparing for the Clinic	Clinical Research
Scientific Training and Development			
Scientist Training / Internships	•	•	•
Technical Staff Training	•		
Scientific Personnel Development	•	•	•
Innovation Science			
hESC Jump Start Initiative	•	•	•
Annual Innovation Grants	•	•	•
Biology of Stem Cells	•		
Egg and Embryo Research	•		
Mission-Directed Science			
New Methods for Development of Stem Cell Lines	•	•	
Stem Cell Based Tissue Engineering in Regenerative Medicine	•	•	
Translational Research	•	•	
Generation and Use of Disease Specific Cell Lines	•	•	
Immune Tolerance	•	•	•
Bio-process Engineering and Automation		•	
Preclinical Product Development		•	
Clinical Investigation			•
CIRM Special Programs			
Disease Teams	•	•	•
Interdisciplinary Research Teams	•	•	•
Tools / Technologies and Infrastructure			
Tools and Technologies	•	•	•
Cores	•	•	
Banks	•	•	
Facilities			
Laboratories / Research Facilities	•	•	
Communities of Science			
Journal / Web Portal	•	•	•
Responsibility to the Public			
Public Outreach	•	•	•
Stem Cell Research and Society: Implications and Impact	•	•	•
Economic Impact	•	•	•

Specific Initiatives

CIRM will undertake the following initiatives, organized according to type of resource. The budget estimate, which is approximate, is based on the number of grants to be awarded, the duration of those grants and the estimated total annual cost per grant.

Scientific Training and Development

Initiative: Scientist Training / Internships

The primary aim of this initiative is to train a cadre of basic and clinical scientists and clinicians needed to expand stem cell research in California. We encourage institutions to make special efforts, consistent with the law, to recruit and retain individuals from many backgrounds, including under-represented minorities.

Total estimated cost - \$157 million

Initiative: Technical Staff Training

CIRM will support training of a technical workforce with skills for stem cell research who will staff the laboratories in non-profit and commercial research institutions.

Total estimated cost - \$38 million

***"The only restraint that
should be placed on funding
is that it must support world-
class science."
-Bill Rastetter,
SPAC Member***

Initiative: Scientific Personnel Development

Because of the restrictions on and uncertainty of federal funding, there is a dearth of young investigators in stem cell research. CIRM will provide both salary and research support for investigators in the early years of their independent careers.

Total estimated cost - \$100 million

Innovation Science

Initiative: hESC Jump Start Initiative

The first CIRM research grant initiative is intended to "jump-start" hESC research in California. This initiative, whose first two RFAs have been issued, will be carried out through programs designed to bring new ideas and new investigators into the field of human embryonic stem cell research; to support mature, ongoing studies on hESCs by scientists with a record of accomplishment in this field; and to create dedicated laboratory space for the culture of hESCs.

Total estimated cost - \$135.3 million

Initiative: Annual Innovation Grants

CIRM will establish an Innovation Grants Program for investigator-initiated grants that will be awarded annually to individual investigators and to research to feed the innovation pipeline. These grants may span the spectrum of basic, translational / preclinical and clinical research.

Total estimated cost - \$148.5 million

Initiative: Biology of Stem Cells

To understand the cellular mechanisms regulating the behavior and fate of stem cells, CIRM will sponsor research to investigate the properties of human and non-human stem cells derived from different sources,

Total estimated cost - \$75.3 million

Initiative: Egg and Embryo Research

CIRM will encourage scientific research aimed at expanding fundamental knowledge of genetic and epigenetic processes that underlie human egg and embryo development, with particular interest is finding new ways to generate human eggs.

Total estimated cost - \$17.7 million

Mission-Directed Science

Initiative: New Methods for Development of Stem Cell Lines

New methods of deriving human embryonic stem cells will enable investigators to generate disease- and genotype-specific cells of many phenotypes. Methods that will not require the donation or use of human embryos or eggs will significantly reduce the medical and ethical concerns that surround current methods.

Total estimated cost - \$12.3 million

Initiative: Stem Cell Based Tissue Engineering in Regenerative Medicine

The use of different types of differentiated cells, along with artificial materials, to create artificial tissues and organs in vitro will be an important future therapeutic result of stem cell research. To develop this field, CIRM will support interdisciplinary research in tissue engineering

Total estimated cost - \$87.4 million

Initiative: Translational Research

The goal of this initiative is to implement a program of grants that will support milestone-driven projects focused on the identification and pre-clinical testing of new therapeutics to accelerate the translation of discoveries in basic stem cell research to treatment in the clinic.

Total estimated cost - \$462.6 million

Initiative: Generation and Use of Disease Specific Cell Lines

The generation and use of disease-specific human embryonic stem cell lines will allow the generation of cellular models of disease that can be used to investigate mechanisms of pathophysiology and for drug discovery.

Total estimated cost - \$30.4 million

Initiative: Immune Tolerance

CIRM will fund an initiative to explore mechanisms for producing large numbers of HSCs either by inducing the *ex vivo* expansion of cells derived from bone marrow or umbilical cord blood, or by deriving them from embryonic stem cell lines.

Total estimated cost - \$60.4 million

Initiative: Bio-Process Engineering and Automation

CIRM will support research in the efficient use of semi-automated and automated bio-processing systems for the production of stem cells and other processes related to stem cells.

Total estimated cost - \$60 million

Initiative: Preclinical Product Development

CIRM will provide funding for preclinical development of specific therapies to investigators in academia and industry and will also provide indirect support through core service and facilities such as regulatory/protocol development services and GMP production. .

Total estimated cost - \$108 million

Initiative: Clinical Investigation

CIRM will contribute to the support of early stage clinical research (Phase I and Phase II) to bring promising therapies and diagnostics to a stage where public and private sector investment would be available.

Total estimated cost - \$451 million

CIRM Special Programs

Initiative: Disease Teams

CIRM will explore a new method of integrating basic, translational and clinical research for a particular disease or group of diseases by funding a team of scientists who will work together over a period of years to develop a therapy based on stem cell research. This initiative will fund work that follows a careful, detailed and plausible strategy with defined milestones for bringing a therapy to clinic.

Total estimated cost - \$122 million

Initiative: Interdisciplinary Research Teams

This initiative calls for the formation of teams that bring together the necessary skills to achieve a specific scientific or clinical goal; we particularly encourage multidisciplinary teams and/or teams formed between investigators in non-profit institutions and in the private sector.

Total estimated cost - \$60 million

Tools / Technologies and Infrastructure

Initiative: Tools and Technologies

CIRM will support tool and technology research and development that can serve the goals of the stem cell community and contribute to the advancement of stem cell science.

Total estimated cost - \$83.3 million

Initiative: Cores

CIRM will address core resource needs important to the rapid advancement of stem cell science. Cores may be in a single, a few or multiple sites, with site, regional and / or state-wide use and may be made available through non-profit and / or for-profit institutions.

Total estimated cost - \$107.2 million

Initiative: Banks

CIRM will establish a stem cell bank that would house and distribute lines derived and characterized using standard protocols and be easily and readily accessible to researchers across the state. The development of a data bank to house information about those lines (and others) would be beneficial as well.

Total estimated cost - \$23.4 million

Facilities

Initiative: Laboratories / Research Facilities

CIRM will offer grants at several levels to meet the space needs for hESC research in California, including grants for new buildings with a substantial amount of space devoted to stem cell research, grants for the construction or renovation of 5,000 - 10,000 square feet and grants for the renovation of shared research laboratories.

Total estimated cost - \$272.7 million

Communities of Science

Initiative: Journal / Web Portal

CIRM will sponsor a variety of mechanisms to enhance communication among scientists and between scientists and the public. These will include databases, a web portal for communication with the public and, with suitable partners, a web-based, immediate access scientific journal.

Total estimated cost - \$5.6 million

Responsibility to the Public

Initiative: Public Outreach

CIRM will support institutional courses or workshops related to public outreach. CIRM will also provide support to develop educational materials and public outreach programs for diverse communities throughout California.

Total estimated cost - \$4.5 million

Initiative: Stem Cell Research and Society: Implications and Impact

Stem cell research not only offers the possibility of medical benefit, but will also influence society in other ways and raises important ethical questions. CIRM will sponsor both empirical research and will also studies or conferences that will take a more theoretical approach.

Total estimated cost - \$25.5 million

Initiative: Economic Impact

CIRM will support studies by independent, outside experts aimed at assessing the economic impact of stem cell research in California.

Total estimated cost - \$2.3 million

Short-term, Mid-term, Long-term Priorities

The priority assigned to an initiative may change over time, for two reasons. The first is its direct impact on CIRM mission's to support the discovery and development of cures and therapies; most of CIRM's initiatives are thus classified as high priority. The second consideration is timing. Different initiatives will be more or less important at different phases of our work. The following table details CIRM's priorities in the short-, medium- and long-term (note that the same initiative may appear in different parts of the table):

	Short-Term Year 1 - Year 3	Medium-Term Year 4 - Year 6	Long-Term Year 7 - Year 10
Highest Priority Initiatives	Banks Biology of Stem Cells Disease Teams Generation and Use of Disease Specific Cell Lines hESC Jump Start Initiative Interdisciplinary Research Teams Journal / Web Portal Laboratories / Research Facilities New Methods for Development of Stem Cell Lines Public Outreach Scientific Personnel Development Scientist Training / Internships Technical Staff Training Tools and Technologies Translational Research	Banks Bio-process Engineering and Automation Clinical Investigation Cores Disease Teams Generation and Use of Disease Specific Cell Lines hESC Jump Start Initiative Immune Tolerance Interdisciplinary Research Teams Journal / Web Portal Preclinical Product Development Public Outreach Scientific Personnel Development Scientist Training / Internships Stem Cell Based Tissue Engineering in Regenerative Medicine Translational Research	Banks Clinical Investigation Disease Teams hESC Jump Start Initiative Immune Tolerance Interdisciplinary Research Teams Journal / Web Portal Preclinical Product Development Public Outreach Translational Research
Other Initiatives	Bio-process Engineering and Automation Clinical Investigation Cores Egg and Embryo Research Immune Tolerance Preclinical Product Development Stem Cell Based Tissue Engineering in Regenerative Medicine	Biology of Stem Cells Egg and Embryo Research Laboratories / Research Facilities New Methods for Development of Stem Cell Lines Technical Staff Training Tools and Technologies	Biology of Stem Cells Bio-process Engineering and Automation Cores Egg and Embryo Research Generation and Use of Disease Specific Cell Lines Laboratories / Research Facilities New Methods for Development of Stem Cell Lines Scientific Personnel Development Scientist Training / Internships Stem Cell Based Tissue Engineering for Regenerative Medicine Technical Staff Training Tools and Technologies

Short-term, Mid-term, Long-term Budget Projections

The development of the Scientific Strategic Plan was accompanied by the development of a financial model. CIRM's projections, while subject to change, are intended to reflect the amount of funding that will be allocated to each category of initiatives over the next ten years. The amounts assigned to each category vary. This variability is the result of many factors, including the number, size, and duration of the grants to be awarded as well as the nature of the work to be performed. The following table details the allocation of CIRM funding across the three segments of our framework.

Initiative	Laying the Foundation	Preparing for the Clinic	Clinical Research	Total
Research Activities				
Scientific Training and Development	Total for Resource Category			\$ 295.0
Scientist Training / Internships	\$ 94.2	\$ 31.4	\$ 31.4	\$ 157.0
Technical Staff Training	\$ 38.0	\$ -	\$ -	\$ 38.0
Scientific Personnel Development	\$ 33.3	\$ 33.3	\$ 33.3	\$ 100.0
Innovation Science	Total for Resource Category			\$ 376.8
hESC Jump Start Initiative	\$ 81.2	\$ 27.1	\$ 27.1	\$ 135.3
Annual Innovation Grants	\$ 89.1	\$ 29.7	\$ 29.7	\$ 148.5
Biology of Stem Cells	\$ 75.3	\$ -	\$ -	\$ 75.3
Egg and Embryo Research	\$ 17.7	\$ -	\$ -	\$ 17.7
Mission-Directed Science	Total for Resource Category			\$ 1,272.1
New Methods for Development of Stem Cell Lines	\$ 8.2	\$ 4.1	\$ -	\$ 12.3
Stem Cell Based Tissue Engineering in Regenerative Medicine	\$ 43.7	\$ 43.7	\$ -	\$ 87.4
Translational Research	\$ 138.8	\$ 323.8	\$ -	\$ 462.6
Generation and Use of Disease Specific Cell Lines	\$ 15.2	\$ 15.2	\$ -	\$ 30.4
Immune Tolerance	\$ 20.1	\$ 30.2	\$ 10.1	\$ 60.4
Bio-process Engineering and Automation	\$ -	\$ 60.0	\$ -	\$ 60.0
Preclinical Product Development	\$ -	\$ 108.0	\$ -	\$ 108.0
Clinical Investigation	\$ -	\$ -	\$ 451.0	\$ 451.0
CIRM Special Programs	Total for Resource Category			\$ 182.0
Disease Teams	\$ 24.4	\$ 48.8	\$ 48.8	\$ 122.0
Interdisciplinary Research Teams	\$ 24.0	\$ 24.0	\$ 12.0	\$ 60.0
Tools / Technologies and Infrastructure	Total for Resource Category			\$ 213.9
Tools and Technologies	\$ 41.7	\$ 41.7	\$ -	\$ 83.3
Cores	\$ 53.6	\$ 53.6	\$ -	\$ 107.2
Banks	\$ 11.7	\$ 11.7	\$ -	\$ 23.4
Communities of Science	Total for Resource Category			\$ 5.6
Journal / Web Portal	\$ 1.9	\$ 1.9	\$ 1.9	\$ 5.6
Responsibility to the Public	Total for Resource Category			\$ 32.3
Public Outreach	\$ 1.5	\$ 1.5	\$ 1.5	\$ 4.5
Stem Cell Research and Society: Implications and Impact	\$ 8.5	\$ 8.5	\$ 8.5	\$ 25.5
Economic Impact	\$ 0.8	\$ 0.8	\$ 0.8	\$ 2.3
Totals	\$ 822.8	\$ 898.9	\$ 656.0	\$ 2,377.7
Facilities				
Facilities				
Laboratories / Research Facilities	\$ 190.9	\$ 81.8	\$ -	\$ 272.7
Totals	\$ 190.9	\$ 81.8	\$ -	\$ 272.7

The amount committed to early-stage research reflects the need to build fundamental knowledge, while funds for the pre-clinical stage reflect the high cost of such research and the growing number of therapies that will be developed with time. Although clinical research is very expensive, its long time course means that most of these costs will occur after the plan's ten-year time frame. The funding allocated to clinical research reflects this, as well as the fact that CIRM will support primarily Phase I trials, where costs are lower, and that CIRM expects to share the costs of later stage Phase II clinical trials with industry.

A Living Plan: Assessment and Revision

- A review will be conducted at years 3 and 7 of the plan by an outside committee of scientists, clinicians, ethicists and patient advocates from within and outside California.
- Assessment will rely on progress reports from CIRM grantees and may include other methods of evaluation such as surveys, interviews, and focus group discussions.
- CIRM may also sponsor a scientific conference to gather information to assess:
 - Whether funding priorities continue to reflect the state of the field in general and;
 - Whether the plan remains responsive to CIRM's mission.
- The review will be reported to the ICOC who will consider the recommendations made in the review and, on that basis, approve modifications to the strategic plan.
- CIRM staff, under the leadership of the President, will propose a 3-4 year operational plan based on the strategic plan as modified by the ICOC.

Introduction

Brief History of the California Institute for Regenerative Medicine

The California Institute for Regenerative Medicine (CIRM) is a state agency created on November 2, 2004 when 59 percent of the California electorate voted to adopt Proposition 71, the California Research and Cures Bond Act of 2004 (Act). The law authorized \$3 billion of General Obligation bonds to fund pioneering stem cell and other scientific research in the state, especially research that the federal government has largely refused to support, for the discovery and development of cures, therapies, diagnostics, and research technologies to relieve human suffering from chronic disease and injury.

The Institute is governed by a 29-member board, the Independent Citizens Oversight Committee (ICOC) comprised of leaders from research institutions and the life sciences industry and patient advocates. At its inaugural meeting on December 17, 2004, Mr. Robert Klein was elected Chairman and Dr. Ed Penhoet Vice Chairman. The board is charged with overseeing the operations and budget of the Institute, including making final decisions on grant awards and on medical and ethical standards to guide research funded by CIRM. Among other achievements, the board hired a President, Dr. Zach Hall, in March 2005, selected a permanent headquarters for CIRM in San Francisco following a competitive process, adopted strict and unprecedented conflict of interest regulations for the ICOC, CIRM staff, and advisors, and created a progressive intellectual property policy for non-profit organizations that receive Institute funding.

In addition to the governing board, three standing, advisory working groups required by the Act were appointed by the board in May 2005:

- Grants Working Group - Responsible for conducting peer review of grant applications and making funding recommendations to the ICOC
- Standards Working Group - Recommends to the ICOC medical and ethical standards to guide the research
- Facilities Working Group - Evaluates and recommends laboratories and other research facilities for funding.

Two lawsuits by opponents of Proposition 71 and embryonic stem cell research were filed in early 2005 to stop CIRM from implementing the law and the will of the voters by charging that Proposition 71 was unconstitutional. The lawsuits had the practical effect of stopping the bond

issuance that was to support the research program. Following a trial in February 2006, however, an Alameda County Superior Court Judge ruled in a legal decision that the Act was constitutional in its entirety and that CIRM was firmly under the management and control of the state. The ruling is being appealed by the plaintiffs and is unlikely to be fully resolved before summer 2007.

Despite this hurdle, on April 10, 2006 CIRM officially became a State funding agency when it announced that the first stem cell grants were awarded. Sixteen California non-profit institutions received a total of \$12.1 million to train the next generation of stem cell researchers as the initial payment of a 3 year commitment. Funding for the 169 training fellowship grants was drawn from the sale of \$14 million of bond anticipation notes (BANs) from six leading California philanthropic individuals and foundations. The California Stem Cell Research and Cures Finance Committee approved the BANs on April 4, 2006. An additional \$31 million in BANs is expected to be announced in November 2006.

The Institute and its board have worked in public meetings and through standard state agency practices to develop the policies, regulations, and infrastructure needed to manage a grant-making program. A Grants Administration Policy – the terms and conditions required for grant awards received by research institutions – was approved by the board in June 2006, and also will become formal state regulations with the force and effect of law. In August 2006, the board approved the final recommended Medical and Ethical Standards regulations, the first comprehensive set of regulations in the nation designed to implement and build upon the recommendations of the National Academies' Guidelines for Human Embryonic Stem Cell Research published in May 2005. All research funded by the CIRM is required to follow this ethical framework, which is in the process of becoming an official state regulation. The Standards Working Group convened 12 public meetings over a year period to develop the recommendations. The development process was characterized by thoughtful deliberation and extensive public comment at every stage. The board-approved intellectual property policy for non-profit recipients of CIRM grants was developed based upon best practices from federal, state, and private foundations with extensive public participation, and is currently in the process of becoming official state regulations with the effect of law. A policy for for-profit recipients of CIRM grants is being developed by a comparable process.

In July 2006, following the presidential veto of federal legislation that would have expanded federal funding of stem cell research, Governor Arnold Schwarzenegger announced that he had authorized the California Department of Finance to loan the Institute \$150 million to jump-start the stem cell research program. With this support, in August 2006 the Institute announced a new grant program focused on innovation in human embryonic stem cell research – the Scientific Excellence through Exploration and Development (SEED) Grant Program and the Comprehensive Research Grant Program. SEED Grants are intended to bring new ideas and new investigators into the field of hESC research and offer an opportunity for investigators to carry out studies that may yield preliminary data or proof-of-principle results that could then be

extended to full scale investigations. Comprehensive Research Grants will support mature, ongoing studies on hESCs by scientists with a record of accomplishment in the field. The Institute anticipates awarding up to \$24 million to support as many as 30 SEED Grants over two years, and as much as \$80 million over four years for up to 25 Comprehensive Research Grants. The board will make funding decisions in early 2007.

Purpose of the Plan

The purpose of California Institute for Regenerative Medicine's Scientific Strategic Plan is to define the long-term objectives that CIRM will pursue and the initiatives it will support to achieve those objectives. The plan, which is intended to address the continuum of stem cell research, will support not only basic, translational, and clinical science, but also ensure a secure infrastructure that will serve as a foundation for future advances. In addition, the plan lays out the mission, the values, and the strategic principles that will guide and underlie CIRM's scientific programs.

***"At the end of the day
it's all about the
patients and the
urgency with which
we need to move
forward."
- Richard Insel,
Juvenile Diabetes
Research Foundation***

CIRM's Scientific Strategic Plan will be a living document which will be revised as CIRM periodically reviews its performance and updates its objectives as new scientific opportunities and challenges arise. The plan sets out milestones at five and ten years on the path to development of treatments and cures for a variety of diseases and conditions. Progress against these milestones will be assessed through review by an outside committee, with subsequent revision of the Strategic Plan. Periodic review and revision will ensure that CIRM remains flexible and opportunistic in adapting to emerging opportunities in the field and the larger environment.

The Scientific Strategic Plan has been constructed to reflect the perspectives and experiences of those who lead the organization along with its various stakeholders who will continue to share their ideas and thoughts regarding the purpose and direction of the California Institute for Regenerative Medicine.

Overview of the Planning Process

The "Plan for a Plan"

In April 2006, the President of CIRM presented to the ICOC a plan for the development of a Scientific Strategic Plan for CIRM (the "Plan for a Plan"). The Plan for a Plan outlined CIRM's

approach to, and goals for, the creation of a working plan to guide the scientific programs of CIRM over the coming years. The Plan for a Plan outlined principles that would govern the planning process, set out the roles and responsibilities of the various groups that would play a part in the plan's development, and described the process and timeline for the plan's creation.

As part of the Plan for a Plan, a Strategic Planning Advisory Committee (SPAC), composed of members of the ICOC, leading scientists, patient advocates, and representatives from the private sector, was formed. (See Appendix A-1 for a list of SPAC members). The purpose of the SPAC was to advise CIRM's President and staff in the development of the Scientific Strategic Plan. The SPAC met regularly during the six month planning process, providing valuable input and insights into the strategic planning process. The SPAC meetings featured an in-depth discussion on one or more topics of interest; most meetings were preceded by the development of an "overview document" to provide background information to help guide the discussion. (See Appendix A-2 for a list of SPAC meeting dates and topics discussed).



A strategic planning team, the Strategic Planning Coordinating Committee (or SPCC), composed of CIRM's scientific leadership and members of the consulting team, was also created. The SPCC's primary charge was to collect, assemble, and organize the information CIRM received during the planning process and to create the first draft of the Scientific Strategic Plan.

Meetings of the Independent Citizens Oversight Committee



The ICOC also played an integral part in shaping the Scientific Strategic Plan. In addition to approving the Plan for a Plan and discussing the plan during the course of its regular meetings, the ICOC also held two special sessions that focused on specific aspects of the plan. The first of these, held on June 1, 2006, resulted in the development of a draft of CIRM's mission statement. The second, held on Aug 1, 2006, resulted in the development of a set of values and strategic principles to help guide CIRM. In addition to providing input into these important

aspects of the scientific strategic plan, various members of the ICOC also attended the scientific conferences and participated in the focus meetings discussed below.

The Data Gathering Process

Scientific Meeting

The data-gathering process began with CIRM's first scientific meeting, which was held on October 1-2, 2005. The meeting, entitled "Stem Cell Research: Charting New Directions for California" was intended to identify scientific priorities for the first phase of stem cell research to be funded under Proposition 71. The meeting featured six scientific sessions and sought to develop, in the words of CIRM president Dr. Zach Hall "ideas for new projects, new approaches, new resources, and new ways of organizing scientific efforts." The outcomes of this meeting, specifically, a series of recommendations from each session for research areas and initiatives CIRM might pursue (See Appendix B), formed the foundation for subsequent data collection efforts.

Interviews

As a second part of the data-gathering process, CIRM conducted a total of 70 interviews with leading scientists, clinicians, scholars, patient advocates, and others. (See Appendix A-3 for additional details on the number and categories of people interviewed or who otherwise provided input into the process.) Interviewees were classified into one of seven categories: private foundation representatives; ICOC members; patient advocates; private sector representatives; prominent scientific / administrative leaders; public interest / government representatives; and scientists / clinicians. The primary purpose of these interviews was to inform CIRM's strategic planning process and ultimately expedite the process of finding cures through stem cell research.

To facilitate the interviews, and ensure that data capture was efficient and consistent, a set of six interview templates was developed. Each template focused on a particular set of questions dealing with: the general goals and objectives CIRM should pursue, the development of embryonic stem cell lines and the ethical, legal, and social issues CIRM will need to address as it moves forward. The interview templates were structured and used in a manner that allowed



each participant to fully share his or her knowledge and expertise, express their opinions, and offer suggestions as to initiatives CIRM might pursue over the next ten years.

Scientific Conferences

In addition to the interviews discussed above, CIRM also conducted a series of three scientific conferences for the ICOC and the public. The purpose of these conferences was to address specific questions related to funding stem cell research and the development of stem cell therapies. (See Appendix A-4 for additional details on the scientific conferences.) Each meeting began with presentations by the speakers (with a question and

answer period) followed by a moderated panel discussion of the speakers built around a series of questions. Each meeting concluded with an open discussion period in which speakers took questions from members of the public. The speakers represented the public and private sectors and offered a wide range of perspective and experiences from which CIRM was able to learn.

Focus Meetings

The fourth component of the data gathering process involved two focus meetings intended to solicit thoughts and opinions, the first from patient advocates and the second from individuals able to speak to the issue of diversity. (See Appendix A-5 for additional details on the focus meetings.) Each focus group was attended by 16 participants, as well as members of CIRM staff and several ICOC members. The discussions, led by one of the participants along with a member of CIRM staff, centered on a series of questions developed specifically for the focus group.



The Development of the Plan

Development of the Plan Outline

The first step in the development of CIRM's Scientific Strategic Plan was the creation of a plan outline. The outline grew directly out of the data collection process and reflected SPCC's understanding of the various inputs it had collected, including recommendations and suggestions by the ICOC. It was based, in part, on a study of the strategic plans of other organizations, including the Wellcome Trust, the National Science Foundation, the National Institute of Biomedical Imaging and Bioengineering, and the National Center for Research Resources, among several others. In addition to careful study by all members of the SPCC, the outline was also reviewed by the SPAC, who voiced their general approval.

Review of Data Collected and Development of Annotated Outline and Related Analyses

With plan outline as a guide, the SPCC team assembled and reviewed the data collected during the planning process (including, but not limited to interview notes; notes and overview documents from SPAC meetings; presentations and notes from the scientific conferences; notes from the focus groups; and transcripts from the ICOC meetings). The outline was then annotated using the data discussed above.

The annotation process involved a careful review of the data, with relevant comments, issues, ideas, and suggestions then added to the appropriate sections of the plan. Particular attention

was paid to the goals and initiatives suggested by the various participants in the data collection process. Additional analyses were conducted on the data to address issues not easily "slotted" into the outline, such as when and how to involve industry and when and how to advance findings into the clinic. This approach was designed to facilitate the writing process by allowing for the development of a more robust outline that articulated specific ideas to "seed" and inform the drafting of the plan.

Opportunities and Challenges

The ability of CIRM to advance its mission will be influenced by multiple opportunities and challenges. Some of these are internal to CIRM and arise from its structure and its history. Others reflect the external environment within which CIRM will work. We discuss several of these and the influence they may exert.

Internal

Opportunities

CIRM can implement new and innovative funding structures.

As a new granting agency, CIRM has the freedom to create innovative funding mechanisms that will encourage creative approaches to stem cell research and therapy development. By observing the experience of other organizations, CIRM can also position itself as a “fast follower”, by imitating successful programs that others have pioneered and by avoiding those that have been less successful. CIRM may thus move toward success more quickly.

CIRM is free to investigate all aspects of stem cell science.

Many states and countries are restricted by laws that prohibit therapeutic cloning. California law, while prohibiting reproductive cloning, does not place restrictions on the creation of new stem cell lines. Proposition 71 calls for CIRM to issue bonds to support "...stem cell research, emphasizing pluripotent stem cell and progenitor cell research and other vital medical technologies...."The ability to focus on embryonic stem cell research without the requirement to limit its efforts to this area gives CIRM a level of flexibility that many others do not have.

"I would urge you not to do the same old thing. You have a chance to innovate and be creative to create structures and programs that meet your strategic needs and the needs of California to pursue particular scientific problems so don't be confined by how other organizations have done things. Be creative and innovate. Do not be conventional or you will be to some extent fostering mediocrity."

***- Michael Rudnicki,
The Canadian Stem
Cell Network***

CIRM has substantial resources and a stable source of funding.

Because the investment by CIRM will be relatively large and funding will extend for 10 or more years, CIRM will be able to pursue opportunities of a size and scope that may not be accessible to others.

CIRM has a highly focused mandate that will allow it to adopt administrative structures and procedures that are specific for stem cell research.

CIRM has the flexibility to hire personnel and to adapt programs specific to its mission of stem cell research. It will thus have the flexibility and dynamism to respond quickly to new opportunities in stem cell science.

Challenges

CIRM has limits imposed by Proposition 71.

Proposition 71 outlines specific limits to the size of CIRM's staff and to its administrative budget. These limits ensure that CIRM will operate economically and efficiently, but restrict the activities that CIRM may be able to carry out. To carry out its mission fully, CIRM will need to be resourceful and imaginative in funding and staffing its activities.

CIRM has a lifespan.

Proposition 71 provides for funding for CIRM through ten years, with a carry-over provision that will allow operation for several years longer. Although ideally the success of CIRM will insure that its lifetime will be extended, this is by no means certain. As the end of its lifespan approaches, CIRM activities may be adversely affected by the prospect of termination.

External

Opportunities

CIRM can become a leader in stem cell research.

By entering the field when it is at a relatively early stage, CIRM has an opportunity to become a world-wide leader. The stability and size of California's financial commitment has already begun - and will continue - to attract top-flight talent to the state at every career level. The growth and quality of the stem cell research community in California will ensure a position of leadership in both the academic and commercial sectors.

CIRM can help define the research and regulatory standards that will shape the development of stem cell-therapies in the US.

By being early in the field, CIRM can help define research and regulatory standards that will guide the development of therapies. Through international cooperation, CIRM can help develop standard protocols for characterizing stem cell lines. It can also work with the FDA to help develop criteria and technology for the testing and use of stem cell therapies.

CIRM can contribute to defining and exploring ethical issues related to stem cell research.

In addition to playing a critical role in setting the direction and standards for research, CIRM can also lead by stimulating ongoing research and discussion on relevant ethical issues, such as oocyte donation, xenotransplantation, and transplantation of cells into human subjects.

CIRM can benefit from, and contribute to, rich research assets of California.

CIRM has the benefit of being located in a state with academic and research communities that are some of the most vibrant in the country and a biotechnology industry that is second to none. As a result, CIRM has access to an extensive set of research resources upon which it may build, allowing it to leverage its funding to produce the greatest possible impact.

CIRM can begin to bridge gaps between people, such as those between basic researchers and clinicians and between academia and industry.

One of the often cited challenges facing researchers today is that their efforts can sometimes be hindered by a "silo" mentality, with investigators in different disciplines or at different points in the research continuum focusing on their own efforts and effectively becoming isolated from one another. This in turn slows the progress of research, as the opportunity to gain valuable, objective insights and "hand off" research to the next stage may be lost. By developing funding and other mechanisms to bring people together and reward collaboration, CIRM can play a role in changing this aspect of the current culture of research.

CIRM can contribute to the development of the stem cell sector of the biotechnology industry in California.

CIRM has a key role to play in catalyzing the growth of the stem cell segment of California's biotechnology industry. The research funding that CIRM provides, along with the critical resources it develops and enables will provide a first "push" to move concepts from the research stage, through development, and ultimately to the marketplace. CIRM can develop ways to foster collaboration between industry and academia, thereby advancing research findings into the development stages and speeding the commercialization process.

CIRM can create new, innovative models for partnerships between the public- and private-sector.

Some models and processes for public institutions to work with the non-profit sector are well established; similarly there are some models for public institutions to work with the non-profit sector. Opportunities will arise for CIRM to create new models for public-private partnerships specifically to advance the field of stem cell research. This is especially important given the strength of California's biotechnology industry and the important role it can play in translating stem cell research into cures, therapies, diagnostics and technologies.

Challenges

CIRM must operate independently of federal funding institutions.

Current restrictions limit the use of federal funding to research that uses approved stem cell lines. Thus, for much of its work, CIRM cannot act in partnership with the largest institution for funding medical research in the world, the NIH. In addition, investigators who use CIRM funds to work outside the federal guidelines must keep this work physically and administratively separate from NIH-funded work. Managing these issues imposes a burden on the scientists, on the research institutions and on CIRM.

CIRM operates in a field that is evolving and dynamic.

Scientifically, the field of stem cell research is quite young, but developing quickly. For example, the publication of the first article reporting the derivation of human embryonic stem cell (hESC) lines occurred in November 1998; between then and December 2004, a total of 132 articles on human stem cells authored by scientists from 97 institutions were published world-wide. The field is evolving very quickly and is also somewhat fractured, which makes it difficult to know what the current state of the art is. Politically, the restrictions imposed by federal and state governments on stem cell research will continue to shape the field; tightening or loosening of these restrictions could have significant short- and long-term impacts on research.

CIRM will have an ever-increasing level of competition world-wide.

A number of countries, among them the United Kingdom, Singapore, Israel, China, and Australia, have vigorous research efforts in stem cell science. Of the 97 organizations mentioned in the preceding paragraph, fewer than 50% are in the United States¹. Additionally, a number of initiatives similar to that launched by Proposition 71 are either planned or underway across the United States, including in New York, New Jersey, Connecticut, Maryland and

¹ Owen-Smith J, McCormick J. An international gap in human ES cell research. Nat Biotechnol. 2006 Apr;24(4):391-2.

Florida, among others. Given the level of activity across the globe, California will not be the sole source of advances being made in the field.

CIRM must manage complex intellectual property issues.

The development of CIRM's intellectual property (IP) policy for for-profit organizations is the responsibility of the Intellectual Property Task Force of the ICOC. While the policy for non-profit organizations was initially approved by the ICOC on February 10, 2006 and adopted on August 2, 2006 (following public comment), the policy for for-profit research organizations is still in development at the time of this writing. When completed, the policy will have a significant impact on the nature of CIRM's interactions and relationships with industry. Given the way in which patents drive therapy development in the for-profit research sector and the requirement that CIRM provide a return to the state, the development of a for-profit policy, and the resulting management of the state's IP interests, gives rise to a unique obligation on the part of CIRM.

***"This is what I mean by
"managing expectations":
making sure everyone
understands the timeline
associated with the
development of complex
biological therapeutic
products."
- Stephen Sherwin,
Cell Genesys, Inc.***

CIRM faces high expectations for therapeutic results.

The public has very high expectations for CIRM, particularly with respect to the time required for the development of new therapies. However, these expectations may not align with timelines required for the development and approval of such therapies. While CIRM has set high goals for itself and will strive to meet the public's expectations, it will be critical that it helps the public understand the nature of the challenges associated with the development of therapies and cures for disease, so that these expectations may be tempered as appropriate.

Mission, Values and Strategic Principles

The Mission Statement of CIRM, which defines our reason for being, expresses the central purpose around which we orient all of our activities. The Values of CIRM represent our deepest convictions as an organization; they are the guiding principles that permeate each of the initiatives that we undertake. Finally, the Strategic Principles form the backbone on which we will construct our Scientific Strategic Plan. Each of these three guideposts was developed and formulated by members of the ICOC.

Mission

In accordance with the mandate of the citizens of California, as specified in the California Stem Cell Research and Cures Act, the mission of the California Institute for Regenerative Medicine is:

To support and advance stem cell research and regenerative medicine under the highest ethical and medical standards for the discovery and development of cures, therapies, diagnostics and research technologies to relieve human suffering from chronic disease and injury.

Values

The values of the California Institute for Regenerative Medicine, which will guide and imbue all our efforts and activities, are as follows:

Accountability. Operating with full responsibility to our stakeholders while upholding transparency and integrity in all our endeavors.

Adaptability. Evaluating resources and opportunities dynamically and responding quickly and flexibly to changing conditions to enhance and improve the speed of discovery.

Collaboration. Fostering joint intellectual efforts and establishing partnerships where appropriate to maximize synergies and increase efficiency and productivity.

Diversity. Empowering all Californians to contribute their ideas and insights to increase chances for success and to ensure that all Californians can benefit from stem cell research.

Excellence. Committing to the highest standards of performance both in our own activities and in the research that we support.

Innovation. Encouraging and rewarding originality to foster new opportunities and advances.

Integrity. Executing all aspects of our mandate according to the highest ethical and moral standards.

Service. Remembering that our ultimate aim is to serve the people of California and others with the research that we sponsor.

Urgency. Constantly maintaining our effort and focus on developing therapies for those who suffer from disease and disability.

Strategic Principles

In addition to the values articulated above, CIRM has also defined a series of strategic principles which will serve as the foundation for all its activities and which will form the backbone of future initiatives:

Providing Funding

Seeding Research: CIRM will catalyze progress by encouraging innovation in new areas of research relevant to stem cell research.

Enabling Research: CIRM will advance research that would not move forward without the Institute's support.

Leveraging Resources: CIRM will seek partnerships with other organizations and with institutions, individuals and other agencies to increase support for stem cell research.

Diversifying Risk: CIRM will effectively balance risky and innovative research with lower-risk research that is more likely to yield returns in the short-, medium, and long-term.

Directing our Efforts

Targeting Critical Gaps: CIRM will seek to identify areas of research and development of therapies in which there is a bottleneck or critical gap that is impeding progress.

Focusing on Translational Medicine: CIRM will balance its support of the stages of therapy development to hasten the movement of laboratory results to the clinic.

Using Comparative Advantage: CIRM will maximize its efforts by capitalizing on the talents and resources within the state that give it a unique advantage with respect to competitors.

Setting and Achieving Targets

Supporting Goal Driven / Directed Science: CIRM will pursue targeted objectives to achieve its mission of developing therapies.

Setting Ambitious Goals: CIRM will set visionary goals that challenge our capabilities.

Achieving Milestones: CIRM will identify and pursue milestones to achieve its mission.

Seizing Opportunities

Sharing Data: CIRM will facilitate the exchange of scientific information among the stem cell research, clinical, and patient communities to advance research.

Capturing Knowledge for Clinical Use: CIRM will use the knowledge gained across all research activities so that the practice of medicine may be improved.

Building Partnerships between Academia and Industry: CIRM will encourage and support collaborations between the academia and industry.

Fostering Dynamism: CIRM will encourage energy, flexibility and innovation in all of its activities.

Strategic Objectives: Aspirations and Commitments

The strategic objectives are the key feature of CIRM Scientific Strategic Plan. They define our goals, both short-term and long-term, expressing our most ambitious hopes and our most realistic expectations. It is the former, our *aspirational* goals that will inspire us and drive us to do more than we thought we could. It is our moon shot, what we dream of achieving. Our more realistic expectations are *commitment* goals that we believe we can achieve, given reasonable good fortune. These are goals that we agree should be used to judge our success in ten years.

CIRM's Aspirations

"A man's reach should exceed his grasp, or what is a heaven for"
Robert Browning in *Andrea del Sarto*

The principle aspirational goal for CIRM is simple: to use stem cells to cure a variety of diseases. In medicine, one rarely speaks of a cure, but because stem cells offer the possibility of replacing diseased or damaged cells and tissues with similar cells and tissues that are healthy, complete cure for the remaining lifetime of a patient is, in principle, possible. The requirements are: the availability of appropriate replacement cells; the ability of the cells to restore complex functions (this may be a special challenge in the nervous system); the stability, including tolerance by the immune system, of the transplanted cells; and the prevention of disease caused by unwanted cell types in the transplanted tissue. As a practical matter, each of these challenges will take time, perhaps decades, to work out completely; in particular, the long-term stability and safety of transplanted cells may take many years to determine. But curing disease remains our ultimate goal.

A second aspiration is to make California the world-wide leader in stem cell research and development, with a basic and clinical research community, spanning the non-profit and commercial sectors, that is unparalleled anywhere in the world. A corollary is that California will be the global center of stem cell research and development for the biotech and pharmaceutical industries.

CIRM's Commitment

CIRM's commitment goals are our covenant with the people of California for what we will accomplish over the next ten years to make the promise of stem cell therapy a reality. Therapy development for clinical use is a long and expensive process. A study conducted by the Center for the Study of Drug Development at Tufts University estimates that development of a small

molecule therapeutic requires 8-10 years and costs in excess of \$800 million². By analogy, it is unlikely that CIRM will be able to fully develop stem cell therapy for routine clinical use during the ten years addressed by this strategic plan. Within that time span, however, we will be able to advance therapies for several diseases to early stage clinical trials, and to have therapies for other diseases in the pipeline ready for clinical development.

To provide a framework for the expression of our ten year goals, we provide a plausible model for the development of a cell therapy, based on analysis of the experience of the pharmaceutical industry in developing small molecule therapeutics. (See Figure 1).

Cell Therapy Development

Stages of Cell Therapy Development

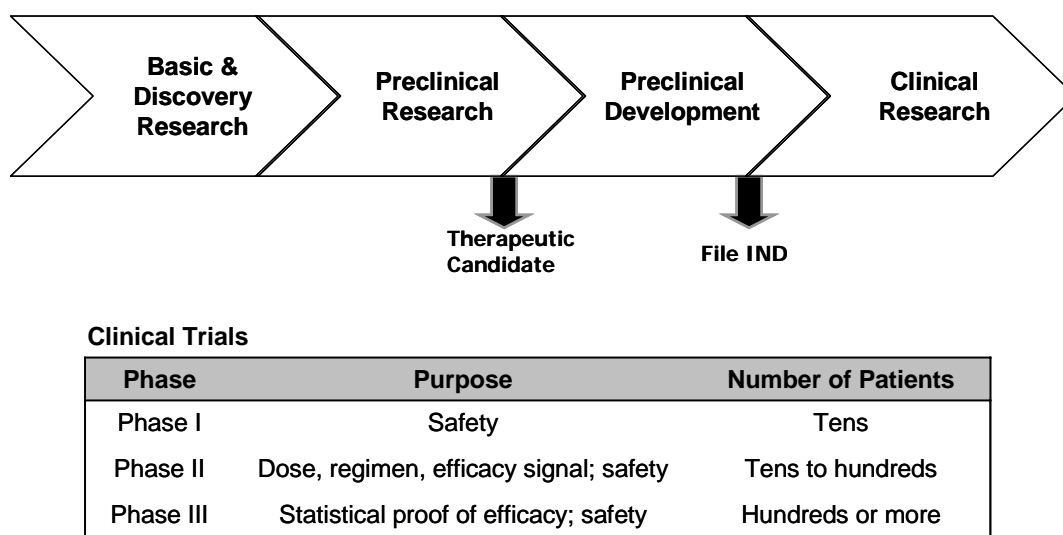


Figure 1: Overview of a plausible cell therapy development process

In the model, development is described as occurring in four discrete stages. The first stage is *basic and discovery research* which provides the foundation for therapeutic development. In this case, it refers broadly to understanding the biology and behavior of stem cells and how to regulate them. For any particular therapy, the time required for this early work is highly variable.

² DiMasi et al. "The price of innovation: new estimates of drug development costs." *Journal of Health Economics* 2003 Mar;22(2):151-85

Because research on human embryonic stem cells is at an early stage (human embryonic stem cells were first reported only eight years ago), much work will be required to lay the foundation for subsequent pre-clinical and clinical studies.

Strategies for disease treatment are then explored in the next stage, *preclinical research*. Preclinical research includes a variety of experiments designed to: identify a possible therapeutic stem cell derivative; develop proof of concept in cell or animal models; conduct pilot safety studies in animals; test methods for small-scale production of the cells and of their delivery; and investigate the fate of the cells in animals. The end-point of this stage of development is the identification of a *therapeutic candidate* for clinical research. This is an important point of decision, as progression to the next stages requires investment of increasing amounts of capital to prepare the specific product for clinical use.

The aim of the next stage, *preclinical development* is to conduct the necessary studies to meet the regulatory requirements for IND (Investigational New Drug) approval by the FDA. Development of large-scale production processes; assessment of purity, potency, stability, activity and safety; and development of a clinical protocol all form part of pre-clinical development.

"If we see hard work is being done, we can manage our expectations. Just don't kill the hope."

- Roman Reed,

***The Roman Reed Spinal
Cord Injury Research Fund***

After IND approval, the final stage, *clinical research*, begins. The most important part of clinical research is testing the efficacy and safety of the treatment in humans through Phase I, Phase II and Phase III clinical trials (see Figure 1 above for the different aims of each stage), but other kinds of patient-based research using the therapeutic cells are also included. Upon successful completion of Phase III clinical trials, a comprehensive Biologics License Application (BLA) is submitted to the Food and Drug Administration (FDA) for approval to market a product.

Preclinical development usually takes 1-3 years, and Phase I and Phase II clinical trials commonly take 1-3 years each. Because the steps are less clearly-defined, the times required in the earlier parts of the time line are more open-ended. Phase III clinical trials, which are the most complex part of the process and also the most expensive (requiring tens of millions of dollars), commonly take 3-5 years. Because of the expense and length of time required, CIRM is unlikely to sponsor a Phase III clinical trial during the ten year period of the plan. If CIRM is successful in its goals, however, others will be motivated to provide the capital and expertise for full clinical development.

Research and development of stem cell therapy for each particular disease will go through the stages outlined above at a pace and time determined by a variety of factors, including how amenable the disease is to a cell therapy approach and how quickly the safety and efficacy of a given treatment can be shown. At any one time, CIRM will be supporting research on many

diseases at different stages of development as well as fundamental research that will set the stage for future therapeutic development.

Ten Year Goals

The ten year time point that we have chosen as the endpoint of the strategic plan is in scientific terms an arbitrary point, a slice or cross section in time of a continually developing process that will go on for many more years as new therapies are developed for more and more diseases and as old therapies are improved. The goal of CIRM at ten years will be to have some therapies in clinical development, with others in the pipeline at various stages of development, poised to go on to the next stage. The goals that we set for fundamental and preclinical research at ten years will be the basis for the continuous development of therapies beyond the endpoint of the plan.

With these considerations in mind, CIRM commits to the following 10 year goals:

Goal I: CIRM grantees will have clinical proof of principle that transplanted cells derived from pluripotent cells can be used to restore function for at least one disease.

Demonstrating proof of principle will require a Phase II clinical trial that gives an indication of efficacy. Such a demonstration will set the stage for large, Phase III, randomized clinical trial(s) with sufficient power to establish proof that the treatment is efficacious and, as appropriate, whether it is better than other treatments that may be available. A convincing demonstration for one disease will encourage and stimulate research on stem cell transplantation for other diseases.

Goal II: CIRM grantees will have therapies based on stem cell research in Phase I or Phase II clinical trials for 2-4 additional diseases.

To ensure a robust pipeline of therapies entering late stage clinical trials, additional therapies will need to progress through Phase I or Phase II trials. One cannot predict at this stage which diseases are the best candidates for early clinical trials. For cell replacement therapy, Parkinson's disease, Type I diabetes, an enzyme deficiency disease (e.g. Tay-Sach's disease; Batten's disease; Gaucher's disease and others), heart disease, spinal cord injury and various types of cancer are among those for which stem cell therapies are being tested or have been considered. Other possibilities include burns and other skin disorders, orthopedic disorders, multiple sclerosis, and neurodegenerative diseases such as Huntington's, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) or spinal muscular atrophy (SMA) in which particular cells in discrete locations are affected. Because stem cell research may lead to other types of therapies besides those based on cell replacement, such as ones based on small molecules, clinical trials may also be in progress for diseases such as Alzheimer's disease or autism in which the affected cell types and their locations are not completely known.

Goal III: CIRM grantees will achieve a level of success that will attract private capital for funding further clinical development of stem cell therapies.

CIRM anticipates contributing to the development of promising stem cell derived cures and therapies with the expectation that at some point, private capital will provide funding for further development, particularly for Phase III clinical trials which will require a capital investment much larger than CIRM or patient advocacy groups can provide. Therefore it will be essential to achieve a degree of success that will encourage the large investment that will carry the research forward. Meeting Goal III will likely be a corollary of meeting Goals I and II.

Goal IV: CIRM will have funded new approaches for achieving immune tolerance for transplantation that are in pre-clinical development.

Immune rejection is a major barrier to transplantation of allogeneic stem cell derivatives into recipients. Chronic immunosuppression, which is the current mechanism for achieving immune tolerance, is associated with infection and other risks that increase mortality. Robust and safe treatments for inducing long term tolerance will be necessary if cell transplantation is to become a widely used therapeutic strategy.

Goal V: Using stem cell research, CIRM funded investigators will have established proof of principle in preclinical animal models for treatment of 6-8 diseases.

Pre-clinical studies in animals set the stage for clinical trials in humans. In addition to the diseases for which there will be clinical trials in humans, CIRM will have established that therapies based on stem cell research are effective using preclinical models of 6-8 different diseases.

Goal VI: CIRM funded investigators will have created disease-specific cell lines for 20-30 diseases and used them to gain new information about pathogenesis, to identify new drug targets and to discover new therapeutics.

Many believe that one of the earliest benefits of stem cell research will be information obtained using disease-specific human embryonic cell lines that bear genes that cause or predispose to particular diseases. In most cases, although the genes may be known, the mechanisms by which they cause cellular pathogenesis are not. Having human cellular models of disease will lead to identification of new genes and pathways that affect pathogenic processes and thus are potential targets for drugs. In some cases, it may be possible to use the cell lines to screen for promising therapeutic compounds.

Goal VII: CIRM will have enabled development of new procedures for the production of a variety of stem and / or progenitor cells that meet GMP requirements. Safe, effective and reproducible production of cells will be important both for laboratory research and for therapeutic purposes. For the latter, large-scale production according to GMP will be necessary.

Goal VIII: Through research sponsored by CIRM and others, a thorough description of the steps of differentiation leading to the production of the various cells of the body will be achieved.

The goal of identifying each of the multipotent intermediates and progenitors that are derived from human embryonic stem cells, including specific markers, is important in being able to direct and control differentiation of stem cells for therapies. A further goal is to understand the changes in gene expression and the epigenetic changes that occur at each step of differentiation.

Goal IX: Through research sponsored by CIRM and others, the factors regulating the self-renewal and oncogenic potential of embryonic stem cells and their derivatives will be identified and characterized.

Understanding the factors responsible for the regulated and unregulated growth of human embryonic stem cells will be important for producing cells and for ensuring their safety. Some understanding of these factors will be necessary at an earlier stage; at ten years, we will have a detailed and comprehensive understanding of growth regulation of pluripotent stem cells, and of various progenitors.

Goal X: CIRM will have enabled development of new methods for tissue replacement based on stem cell research.

Tissue engineering, the use of cells and bio-compatible materials to form artificial tissues will be a logical next step for regenerative medicine. By combining one or more different cell types derived from stem cells with natural or artificial materials, artificial tissues can be formed that can be used to replace or repair damaged tissue in the body. Understanding how to do this will require the close collaboration of biologists, bioengineers, material scientists and clinicians.

Five Year Goals

These goals will be used as milestones to gauge our progress toward our ten year goals

Goal I: CIRM grantees will have six therapies based on stem cell research in pre-clinical development.

To achieve our ten year goals of having therapies in the clinic, it will be necessary to have therapies for at least six diseases in late stage clinical development by the end of five years, with others poised to begin clinical development.

"We need more than just home runs. We need singles and doubles that may impact the lives of patients. These may not be cures but they will impact their lives."

***- Ethan Singer,
High Q Foundation***

Goal II: CIRM grantees will have developed new methods of making stem cell lines.

Developing new methods of deriving stem cell lines is an early goal. There is particular interest and urgent need for methods that can be broadly applied to obtain lines with desired genetic properties, particularly those that predispose to disease; there is also an urgent need for methods that do not require human oocyte donors.

Goal III: CIRM grantees will have successfully created disease-specific stem cell lines for four diseases.

Using techniques that are currently available and those to be developed, a concerted effort will be made to derive embryonic stem cell lines that are disease-specific. As described above, disease-specific lines are potentially powerful tools for disease research and drug discovery.

Goal IV: CIRM grantees will have developed methods of growing stem cells in defined media.

This is an important technical problem. The use of defined media for growing stem cells and the cells that are derived from them will be an important step toward therapeutic use of the cells.

Goal V: CIRM will have enabled establishment of a stem cell bank.

Establishing a stem cell bank for characterization, storage and distribution of stem cell lines made by CIRM investigators will be essential for research and therapy.

Goal VI: CIRM funded investigators will have demonstrated methods for inducing immune tolerance in animal models.

Addressing the clinical problem of rejection of transplanted tissue by the recipient's immune system would be of wide-spread benefit for cell replacement therapy, as well as for solid tissue transplantation, bone marrow transplantation, and autoimmune disease. Methods for inducing tolerance will need to be investigated first in animals.

Goal VII: CIRM will have increased the workforce of stem cell researchers in California.

Through its training programs and through the recruitment of scientists to California, CIRM will augment the number of basic, translational and clinical scientists, as well as the number of trained technical staff. CIRM will strive to increase the diversity of the work force at all levels.

Goal VIII: CIRM grantees will have established tools for toxicity testing based on stem cell research.

Stem cells are potentially useful as a method of screening drug candidates for toxicity in humans. Identifying compounds that are toxic for humans at an early stage will shorten the time and diminish the cost of drug development.

Goal IX: CIRM will have established effective partnerships in stem cell research between scientific teams in non-profit and commercial sectors.

Collaboration between researchers in non-profit institutions and those in private companies will be essential to the success of stem cell research and therapy.

Goal X: CIRM will have established national and international collaborations in stem cell research.

To achieve its goals, CIRM will seek partners outside of California with whom it can collaborate in the development of therapies for disease.

The Strategic Planning Framework

CIRM will achieve its strategic objectives through a series of initiatives that, taken together, will define the CIRM research program. Before describing the initiatives in detail, it is helpful to consider the overall context of our program so that the orientation and purpose of each initiative within the program can be understood. Because the size and complexity of the program make it difficult to represent in a simple or linear way, we have chosen to lay out two sets of orthogonal coordinates that define a “space” within which each project and initiative can be located.

The first horizontal coordinate reflects the pathway leading from basic science to the clinic, with three sequential segments: Laying the Foundation; Preparing for the Clinic; and Clinical Research. Below, in the section entitled Charting the Path to Therapies, we discuss the relevant challenges, needs and aims of each of the segments and how they are related to the values, strategic principles and long-term goals of the plan. (See Figure 2)

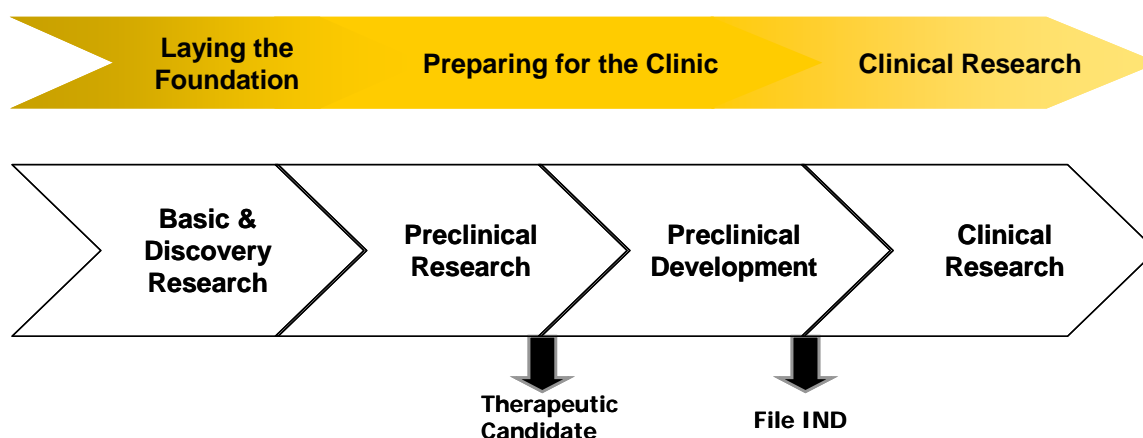


Figure 2: The pathway from basic science to the clinic

The second vertical coordinate is organized according to the different resources that we will draw on: Scientific Training and Development; Innovation Science; Mission-Oriented Science; Tools, Technologies and Infrastructure; Facilities; Communities of Science; and Responsibility to the Public. This axis is represented as orthogonal to the progression from basic science to the clinic since resources in each category will form the underpinning of all three domains of the progression from basic science to the clinic. The needs and aims with respect to each of these resources are also discussed below. (See Figure 3)

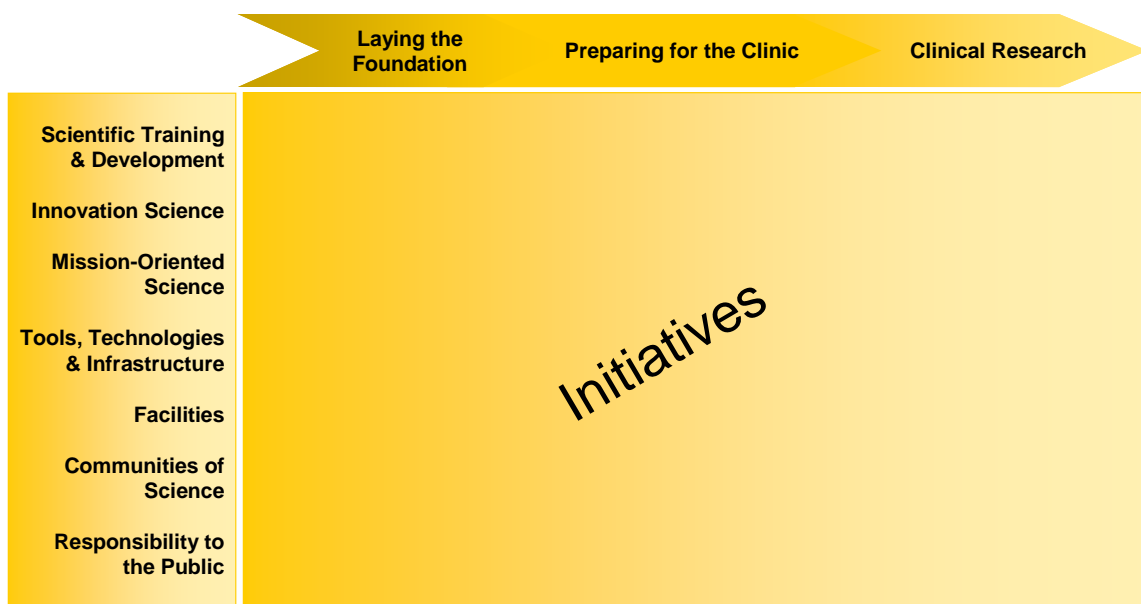


Figure 3: Resources that will underpin the pathway from basic science to the clinic

The usefulness of this arrangement is that each initiative that we discuss in later sections can be given a position within the two-dimensional diagram. By orienting them and discussing them with respect to each axis, we are able to give a richer context to the initiatives that we plan.

Charting the Path to Therapies

Laying the Foundation

There is general agreement that before human embryonic stem cells can be developed for widespread clinical use, much work on their fundamental biology must be done. Until we understand how to produce specific types of cells safely and efficiently for transplantation, we will be unable to carry out our clinical programs. The effort to obtain such knowledge will direct much of CIRM's early research program. Many of the questions that CIRM will attempt to explore are outlined in this section. In all cases, the imperatives are shaped by the ultimate therapeutic aims of our program.

What are embryonic stem cells?

An early challenge is to understand what defines an embryonic stem cell and how different human embryonic stem cell lines differ from each other and from stem cells isolated from other sources, such as cord blood, fetal and adult tissues. Comparisons of the human embryonic stem cell lines now available are proceeding, along with efforts to establish standard

characterization protocols that will allow stem cells isolated in different laboratories and by different procedures to be compared in a systematic way. Early indications are that not all lines are the same. Do these differences reflect intrinsic distinctions between very early stem cells that have different capabilities or do they indicate mutational or epigenetic changes that have occurred during isolation and passage? To understand the basis of the variations between stem cells we will need to make more human embryonic stem cell lines and to characterize them very early after isolation. As we learn more about the taxonomy of embryonic stem cells during these early stages, we will better be able to monitor changes that occur as lines are carried through many generations. An important practical consequence will be standardized and optimized ways of culturing and propagating human embryonic stem cells.

Neither stem cell self-renewal nor differentiation is well-understood.

The two characteristic features of embryonic stem cells are their almost unlimited capacity for self-renewal and their ability to differentiate along multiple lineages to produce the wide variety of specialized cells found in the adult. Our understanding of the cellular and molecular basis of each of these important properties is incomplete. Although much of the necessary work will be done with human cells, critical insights into the biology of stem cells will continue to come from work on model organisms, such as mice, fruit flies (*Drosophila melanogaster*) and roundworms (*Caenorhabditis elegans*).

We are just beginning to understand the mechanisms and regulation of self-renewal in stem cells. Because this property allows large number of cells to be produced by expansion in vitro, understanding it is crucial for the production of cells for therapeutic use. Understanding self-renewal may allow manipulations to confer this property on other types of progenitor cells, such as adult or cord blood stem cells. Self-renewal can be a dangerous property, however, since unregulated self-renewal in vivo results in tumors. Understanding and controlling self-renewal is thus a key to assuring the availability and safety of cells to be used in therapies based on the transplantation of stem cells or their derivatives.

The second signal characteristic of embryonic stem cells, their ability to differentiate along multiple pathways, is also insufficiently understood, particularly for human embryonic stem cells. Evidence from animal systems demonstrates that differentiation occurs in a step-wise fashion along defined pathways with distinctive decision points. Scientists need to define the pathways and to understand the genes, factors and signaling systems that determine the choices stem cells make. Although studies in animals cannot be directly translated to humans, they are important in providing general principles that can speed subsequent studies with human cells.

A long-term aim of basic stem cell research is a lineage diagram that will show the complete set of differentiation pathways that generate the various cells of the body with each of the intermediate cell types identified and defined and the critical factors delineated for each decision point. Such a diagram will be possible only if there are methods for identifying each of the cell

types in the pathways. Except in specialized areas, such as hematopoiesis, there is currently a lack of reagents for identifying and separating cells in the human lineage. Other important questions concern how the choice between self-renewal and differentiation is determined at each step and what determines whether division is symmetric or asymmetric.

Many types of stem cell lines are needed.

The generation of new human embryonic cell lines will be important for answering these questions, but will also be important for other reasons. If stem cells are to be used as therapies, it will be important to have available a large number of stem cell lines of diverse genetic backgrounds that represent the range of human populations and to understand the influence of these backgrounds on their properties. In particular, as discussed below, the availability of embryonic stem cell lines with genetic mutations that lead to disease will be a powerful tool for understanding the cellular basis of pathogenesis for many disorders.

The most prevalent method of obtaining stem cell lines, which is from blastocysts (and in some cases, from morulas, or embryos at the eight-cell stage) that have been created by in vitro fertilization for reproductive purposes, is an inadequate source to meet research and therapeutic demands, as desired genetic characteristics cannot be easily obtained. A method of generating embryonic cell lines from adult cells (taken from the mucosa of the cheek, for example) would be of enormous advantage. One possibility is through nuclear transfer, a technique that works in a variety of mammals and is likely to work in humans. Nuclear transfer, like the derivation of embryonic stem cells from blastocysts, however, requires egg donation, a technique that exposes women to medical and psychological risk. Other techniques for nuclear reprogramming that do not require egg donation should be intensively explored.

Because current and immediately anticipated (e.g. nuclear transfer) methods for deriving stem cell lines require egg donation, CIRM will need to pay close attention to the associated ethical and legal issues. In particular, it will be important to build ethical and medical studies into research programs in which eggs are donated. On the one hand, there will be opportunities to obtain information about medical and psychological risks. On the other, investigation of the effectiveness of methods of obtaining donor consent may help guide future policies.

Stem cells respond to their environment.

In vivo, the behavior of stem cells is importantly regulated by interactions with their immediate environment. In the body, stem cells occupy special locations, or niches, whose components interact with stem cells to regulate cell division and to influence differentiation. Understanding the role of the niche is important in guiding in vitro attempts to regulate stem cells; it is also important for understanding the behavior of endogenous stem cells and of stem cells and their derivatives that are introduced into the body. Thus methods may be devised to activate and engage endogenous stem cells for therapeutic purposes. This may be of particular interest in

the brain where endogenous stem cells have been shown to home to sites of injury. Understanding of the role of the niche may also lead to the construction of artificial environments for stem cells, to be used either in vitro or in vivo.

Stem cells are potential tools for discovery.

In addition to their use in cell replacement therapy, stem cells are potentially powerful tools for developing and delivering other kinds of therapies for disease and disability. Stem cells can serve as vehicles of delivery for growth factors, enzymes and other cellular products, for replacement of missing factors or for other therapeutic purposes. Differentiated cells of differing genotypes could also be very useful in toxicity testing. By far the most important potential research application, however, is to use stem cells to create cellular models of disease by creating new cell lines with genes that cause disease. Such cell lines could be used to produce specialized cells known to be affected in the disease (e.g. spinal motor neurons for ALS, oligodendrocytes for multiple sclerosis). Such human cellular disease models could be powerful tools for investigating the cellular pathophysiology of the disease, for identifying new targets for drug development, or for screening for drugs that could give phenotypic rescue.

To realize the potential of stem cells, it will also be necessary to develop techniques for their manipulation. We will need to have methods of introducing genes or of screening for small molecules to regulate their self-renewal or to drive them down different pathways of differentiation.

Tissue engineering is an important part of regenerative medicine. Regenerative medicine includes both cell therapy and tissue engineering, in which replacement organs or tissues are grown in the laboratory. In tissue engineering, different kinds of cells may be combined and the aggregated cells given shape and organization through the use of artificial supporting structure and/or biomolecules. As we gain more control over the growth and differentiation of stem cells, the possibilities of creating artificial tissues and organs are greatly expanded. Using stem cells for cell replacement therapy is thus only the first step in a more ambitious program of regenerative medicine which will be developed over the coming decades.

Preparing for the Clinic

Although everyone understands the importance and promise of clinical studies and most understand the need for fundamental knowledge about how to derive and direct stem cells along specific pathways, the need and importance of pre-clinical research and development often goes unrecognized. Before a potential therapy that has been developed in the laboratory can be used on humans, it must be shown to be effective and safe in model systems. Although cellular studies can give some information, investigations in animals provide better information. Ideally, the agent must be shown to have efficacy in an animal model of the disease for which it is a treatment. Also, a series of tests are required to demonstrate the safety of the agent in animals. Additionally, once a specific product is identified and is being readied for testing in

humans, the production and quality of the therapeutic agent itself must be assessed. How it was produced, what materials and protocols were used (GMP), how reproducible is production from batch to batch, what is the level of purity and the processes for assessing and assuring a quality product (Quality Assurance (QA) and Quality Control (QC)) – all of these questions become important.

The use of stem cells as tools may also lead to the discovery of new therapeutic compounds or biologicals that can be developed for clinical use. Although the development of promising therapies that arise in this way is no less important, the pathways for pre-clinical development of these therapies are relatively well-defined. For these reasons, our discussion focuses on the particular challenges of cell-based therapies.

"It takes a long time and a lot of money to take an idea from the lab and advance it through development and put it in the hands of doctors and patients. It will take longer and cost more than anything you can possibly imagine, so you need to plan for that."

***- Stephen Sherwin,
Cell Genesys, Inc***

Preparation and characterization of cells for therapy is a first step.

Optimally, preparation for pre-clinical development begins in the laboratory. The body of standards known as Good Manufacturing Practices (GMP) is the FDA's way to ensure that an investigational therapy intended for use in humans is produced so as to be of consistent quality. GMP includes standard operating procedures (SOPs) which provide detailed protocols for and documentation of all materials and procedures that are used in the production of a cell therapeutic to be used in humans, as required by the FDA. Thus, if therapeutic use of a cell line is contemplated, ideally, GMP procedures should begin with its derivation and be followed for all subsequent steps. Minimally, a cell line intended for use in humans must be able to document the processes and reagents used in its derivation and maintenance. GMP production of a cell therapeutic for investigational use in humans and for IND-enabling safety studies will be an important consideration throughout pre-clinical and clinical development.

An early challenge for pre-clinical development of therapies based on transplantation of stem cells will be to develop methods for scalable production of the cells in GMP facilities. Optimal conditions for growth, harvesting, purifying and storing cells will have to be determined for each cell type. Product characterization will be a special challenge, as standard methods for assessing the cellular homogeneity of stem cell preparations are not well-established. Markers that will distinguish between desired and undesired cells will have to be developed as will acceptable criteria for levels of contaminating cells. Finally, product specifications will have to be established to define the batch-to-batch characterization needed to ensure comparable product.

Efficacy, activity and safety of stem cell preparations will need to be tested in animal models. Such studies may include determination of the best route of administration, transplantation site, and cell fate and seek answers to questions such as the following: Where do the cells go and how long do they survive? Do they continue to exhibit the desired function (e.g. secretion of dopamine or insulin for Parkinson's or Type I diabetes, respectively)? Is there restoration of function and does it last? Most importantly, will administration of the cells be safe? As stem cells undergo repeated rounds of replication as their numbers expand during production, cells in the populations will accumulate mutations, some of which could be harmful. Because tumor formation is a danger, rigorous estimation of the possible complications arising from transplantation using animal models may take many months.

Developing supporting technologies will be important for the ultimate success of cell replacement therapy.

To bring stem cell therapy to widespread use in the clinic, other problems besides those of cell preparation and use will need to be addressed. One important problem is immune tolerance. Currently, for allogeneic transplants, immune suppression is required to prevent rejection of the tissue by the recipients, leading to unwanted and sometimes life-threatening complications. For some indications, patient-based stem cell lines offer a potential solution. However, the expense and difficulty of creating a tailor-made cell line, at least by current methods, makes this solution unlikely to be practicable on a large scale. Also for diseases such as Parkinson's disease or Type I diabetes, in which the newly introduced cells would presumably be susceptible to the same pathogenic processes as those they are meant to replace, patient-specific cell lines presumably offer no advantage.

A general solution to the problem would be most desirable. One possibility is to replace the immune system to make it compatible with the transplanted cells that are being introduced. For example, for Type I diabetes, new hematopoietic stem cells could be introduced along with new insulin-producing cells, both derived from the same embryonic cell line in order to prevent immune rejection. Other strategies to overcome immune rejection may also be possible. Early experimentation to show proof-of-principle in animal models (mice and/or primates) will be necessary before studies in humans will be possible.

Other technological needs for development may include: new methods of introducing cells; the creation of artificial niches to contain the introduced cells; automated methods of growing cells; bioreactor and process engineering for large-scale production.

Novel mechanisms for support of preclinical research and development need to be explored.

Pre-clinical development poses a further challenge in that the institutional and financial support mechanisms are less well-defined than for basic and clinical science. Basic science occurs in non-profit research institutions, funded largely by the federal government and, to a lesser extent,

in biotechnology and pharmaceutical companies. Large-scale clinical trials, now mostly funded by the pharmaceutical companies, can occur either in academic settings or in non-academic settings, usually organized by industry. Pre-clinical development is in general not funded by the federal government and occurs in large pharmaceutical firms and in biotechnology companies. In large, well-capitalized companies, pre-clinical development can be easily financed, but in small companies, where much early-stage development occurs, the ability to carry out pre-clinical development for a promising treatment is often the difference between success and failure. Pre-clinical development is essential to satisfying FDA requirements and for attracting the necessary capital for clinical trials.

If CIRM is to be successful in bringing therapies to the clinic that are based on stem cell research, we will need to address the problems posed by pre-clinical development. In some cases, this may mean developing new funding mechanisms to accomplish our aims. Large pharmaceutical companies are not yet willing to make major investments in stem cell research. Thus, it seems most likely that preclinical development will be carried out by small companies, often in partnership with academic scientists. A major challenge will be to educate academic scientists with respect to preclinical and clinical regulations so that discoveries in academic laboratories can move as smoothly as possible into pre-clinical development.

Clinical Research

Ultimately, any potential stem cell or stem cell derived cure or therapy must be rigorously tested in human subjects before it can be made broadly available to patients. Clinical studies are designed and conducted to address safety, dose, delivery, mechanism, regimen, and efficacy with the ultimate goal of developing a cure or therapy that can benefit patients. Similarly, tests or diagnostics that may be derived from stem cells must also be the subject of clinical research, sometimes with human subjects and sometimes with samples from human subjects.

Clinical trials, which test outcomes of the use of therapeutics or procedures, are conducted in three sequential phases: Phases I, II and III. Each phase builds on the information gathered in the previous phase and is designed to generate additional information about the candidate therapy. Figure 4 summarizes the relevant features each phase.

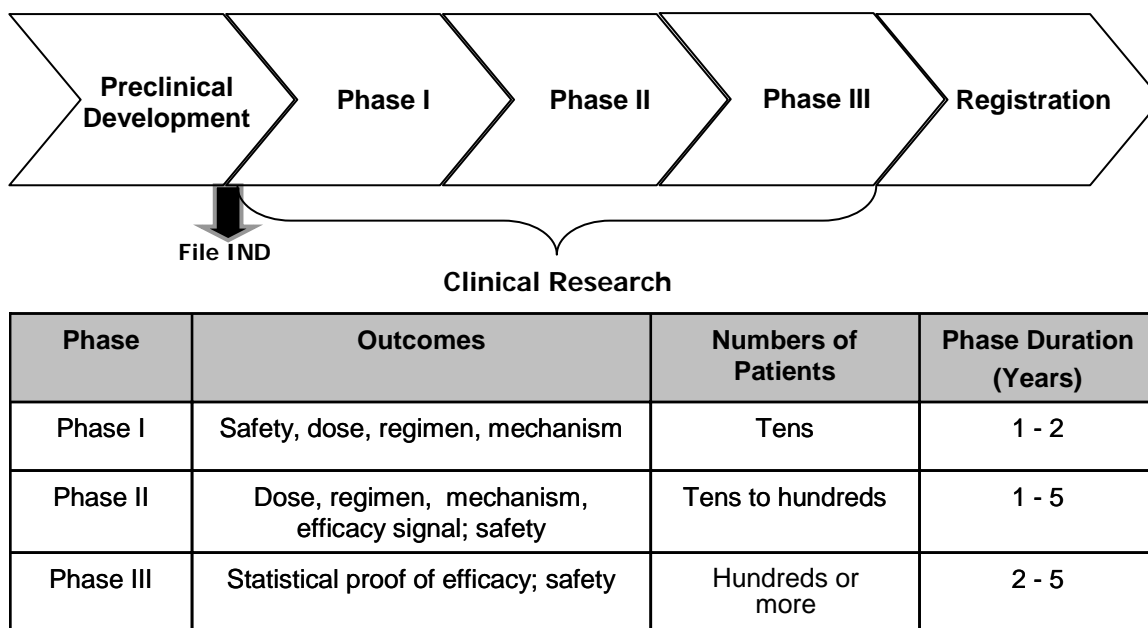


Figure 4: Features of clinical trials

Phase I trials will form the core of CIRM's clinical trial program

Especially with new and/or complex therapeutic modalities, such as therapies using cells derived from pluripotent stem cells, many early pilot Phase I-like studies may be conducted. These studies are typically conducted in normal volunteers or in patients, depending on the disease indication and the risk of the therapy; in the case of a new modality such as stem cells, such studies will likely be conducted in patients. Phase I studies conducted in patients that also seek to assess activity of the therapy are typically called Phase I/II studies, but will be included in this document as part of Phase I stage of clinical investigation. Such pilot clinical studies trials may, for example, test delivery methods or methods to monitor cell localization and/or activity. Although CIRM will fund some Phase II trials, most clinical trials undertaken over the ten year time span of the strategic plan will be Phase I trials whose purpose will be to evaluate and refine novel cell therapies, readying them for the more focused clinical development leading to product registration and approval. Some of the Phase I trials will be conducted by investigative groups at academic medical centers (AMCs); others may be conducted by private companies, often in partnership with AMCs. Through its grants programs, CIRM will need to encourage collaboration between investigators at AMCs and those in industry.

The AMCs and the smaller companies who often lead in the development of innovative therapeutic modalities are finding it increasing difficult to fund early stage clinical research for very novel therapies. AMCs have difficulty due to shrinking of the NIH budget and decreased clinical margins resulting in less discretionary funding for research and for support of the

physician-scientists who conduct such research. The smaller companies who focus on stem cell based therapy development have difficulties in attracting funding due to the general unwillingness of the pharma / biotech industries and the venture capital community to fund research for innovative therapies where the business model is not well-developed or tested. CIRM's ability to fund preclinical and clinical research at AMCs and companies will be an important contribution to advancing stem cell therapy development.

Research with human subjects is regulated both nationally and locally.

"People who are passionate about curing these diseases tomorrow need to understand we will only set the field back if we plunge in and do it in a premature way. We need to move ahead with all speed but with diligence, with rigor, and with safety in mind.

***- Allen Spiegel,
Albert Einstein College
of Medicine***

Clinical research, because it involves research on human subjects, is heavily regulated. In the U.S., the Food and Drug Administration (FDA) has regulatory authority over such activities. The FDA requires that a therapeutic candidate to be tested in humans be produced by well defined, documented, reproducible procedures that result in lot to lot consistency of a product that meets standards of purity, identity and potency. GMP is the acronym given to the set of practices and standards that lead to a production of a candidate therapeutic that meets FDA regulations. Because the field is new and will be developing rapidly, FDA regulations may be expected to evolve. By maintaining communication with the FDA, CIRM and CIRM-funded investigators can play an important role in aiding the emerging development of the standards.

Additionally, in order to help ensure that any new therapeutic intervention that goes into people is safe and affords potential benefit, institutional review boards (IRBs), as well as the FDA review all proposed clinical studies involving human subjects. They assess the proposed studies, in the context of preceeding non-clinical and clinical studies, to ensure, as far as possible, the safety of human subjects in light of potential benefit. They may also address whether the study is designed to provide clear answers to the questions being addressed by the research.

Clinical research is a complex endeavor.

Because it involves human subjects, clinical research is arguably the most difficult form of biological research. Subjects must freely and voluntarily consent to the trial; every precaution must be taken to minimize risk to the subject; and there must be the prospect of potential benefit. To maintain these standards, clinical research is necessarily complex. It involves a supply of a GMP-produced therapeutic; an understanding of, and compliance with, the regulatory requirements for research in human subjects; a clear understanding of what question(s) to ask in a study; a well designed study; timely access to patients; access to the

medical and support professionals to treat patients and record their responses to therapy; and finally, access to data management and analysis professionals who analyze the data and provide results to medical professionals for their interpretation. Clinical research with intent to register a therapeutic candidate for marketing approval is still more complex. Typically, the end game, that is, the label claim allowed by the FDA upon product registration for a desired benefit for a given patient population, is decided upon in preclinical development or early in clinical research. Subsequent clinical research is undertaken to realize the desired claim for benefit to patients, and, importantly, to establish safety.

Developing and Enabling Critical Resources

To accomplish the aims and objectives that are set out above, CIRM will have to develop and use resources of many different kinds. These resources may be thought of as constituting an orthogonal axis to the progression from basic science to the clinic, since the resources in each category will contribute to all three domains discussed in the previous section.

Scientific Training and Development

There is a critical need for trained personnel in human embryonic stem cell research at all levels. The restrictions on federal funds have severely limited the number of laboratories and laboratory personnel working on human embryonic stem cells. The scarcity of funds has particularly discouraged new investigators who are beginning their independent careers. The research planned by CIRM will require a large expansion in the number of trained scientists in this field. Basic, translational, and clinical scientists trained in stem cell science are all in short supply. Trained technical staff will also be needed. To pick two examples, the culture and maintenance of stem cells requires special technical skills, as does the micromanipulation of single cells used to develop new stem cell lines. It will thus be important for CIRM to sponsor training programs in stem cell research at both the professional and technical levels.

***"There is a desperate need
to attract bright people
into this discipline."
- Garret FitzGerald,
University of
Pennsylvania***

Through the training programs that it sponsors, CIRM will have an important opportunity to encourage and expand diversity in the stem cell work force at all levels. Although important in all contexts of stem cell research, diversity in scientific personnel will be especially critical as research progresses into the clinic, where minority scientists and staff will be key for enrolling minority populations in clinical trials, which is often a challenge.

In addition to training intended to increase the numbers of people in the field, there may be opportunities for specialized training programs for those who are already working on stem cells. Two possible examples that have been suggested are: training programs in how to make

human embryonic stem cell lines; and training for translational and clinical scientists in regulatory standards and requirements for cell-based therapies.

Innovation Science

An important part of CIRM's program, especially in the early years, will be to encourage investigator-initiated, curiosity-driven science that is relevant to the development of stem cell therapies. Although much of CIRM's research program will be shaped by initiatives with specific goals, the free inflow of new ideas must be maintained. Creative ideas by their nature cannot be predicted, nor can the emergence of new technologies. Because there is much that we do not know about stem cells, we cannot chart the exact course by which we will solve the problems and achieve the milestones that are necessary for success. To fully exploit the creative energies of California scientists, we will need to have as part of our research program broad initiatives that will allow scientists to obtain funding to explore new ideas or new techniques that we cannot now know or predict.

Traditionally, curiosity-driven research has been supported by R01 grants at NIH in which investigators propose research based on a new idea or a new opportunity that they conceive. Over the last half century, this mechanism has been remarkably successful in generating new and unanticipated discoveries that channel research into new directions. To take two examples: first, the discovery of restriction enzymes in bacteria gave rise to recombinant DNA technology which has transformed biomedical science; second, the investigation of cell death during development in the roundworm *C. elegans* led to fundamental insights into the active regulation of mechanisms of cell death in cells from many organisms, including those of humans. The limited federal support for innovation science on stem cells makes it very imperative that CIRM support open-ended, investigator-driven research related to stem cells as a key element of its overall program.

***"There will be important
successes that none of us
can predict."***

***- Susan Fisher,
University of California,
San Francisco***

Although often associated with basic research, investigator-initiated, curiosity-driven research can occur anywhere along the trajectory from the bench to the bedside. Creative, new ideas for growing or delivering cells and patient-based research that seeks to understand disease mechanisms or transplanted cell fate are preclinical and clinical examples, respectively of innovation.

Initiatives that allow investigators to suggest new ideas, approaches or problems will be an integral part of CIRM research program at all stages in the progression to the laboratory to the clinic. As work progresses toward therapy and becomes more directed to specific aims, the emphasis on curiosity-driven research will diminish. Because of its importance in generating

new discovery, however, curiosity-driven science will clearly need to be part of CIRM program over the next ten years.

Mission-Directed Science

Although scientific understanding provides the foundation, the main thrust of CIRM's research is to develop therapies. Thus, a substantial body of CIRM research will support research projects directed toward specific ends. The goal may be to find and test a therapy for a particular disease, to generate a tool, or to solve a specific technical or scientific problem that is necessary for progress toward therapy. CIRM will deploy both grants and contracts in the support of mission-directed science, and, as indicated by the examples, the particular mission may related to basic, translational or clinical goals and may involve a small problem or a large one. Grants or contracts will be used to achieve the specific aims, which will be spelled out in the call for applications (RFAs or RFPs).

The specific aims to be achieved will be identified through consultation with the scientific community by a variety of mechanisms. One purpose of CIRM Conference "Stem Cell Research: Charting New Directions for California" and the numerous interviews and meetings carried out during development of the scientific strategic plan was to identify specific opportunities or roadblocks to progress that would form the basis of research initiatives. Many of these appear in the initiatives section of this document. In other cases, CIRM has insufficient information at present to make a judgment about whether or not an initiative directed to a particular end is needed or is timely. In these cases, workshops that gather experts for discussions of particular topics will be used to identify pressing needs or unusual opportunities. CIRM will continue to hold workshops and conferences, as needed, throughout the term of the plan to learn about, develop and evaluate ideas for specific, mission-oriented initiatives.

***"Synergy will have to be rewarded because no one place will be the "it" or be alone in providing the answers and breakthroughs in the stem cell arena. We can't afford a silo mentality."
- James Gavin,
Emory University***

CIRM Special Program Initiatives

CIRM Special Program Initiatives are those in which the Institute proposes to organize funding in new and unconventional ways in order to promote progress. The hallmarks of the first initiatives in the program will be an emphasis on:

- Collaborative teams
- Specific goals with a timeline and milestones
- Active management of the project
- Active CIRM participation in evaluation and project management

Some of these teams (Disease Teams) would focus on bringing basic, translational and clinical scientists together over a period of years to develop therapies for a specific disease. Others (Research Teams) would be interdisciplinary teams that bring together investigators with different expertise (cell biologists, engineers, chemists or others) to solve specific problems. Teams can consist of members from both non-profit research institutions and from private companies.

Teams will be organized to attain specific goals within a given time line. The project will be actively managed by a project manager. Progress will be evaluated and strategy modified as necessary by an advisory group that includes members of the team, outside scientists, and CIRM personnel.

Tools / Technologies and Infrastructure

Many of CIRM initiatives will be directed toward projects to develop specific tools, enabling technologies, or infrastructures that will support the basic, translational and clinical science needed to develop therapies. Some tools that are needed can be identified and produced in a straightforward way – a panel of monoclonal antibodies or other labels that can be used to identify and separate specific kinds of stem and progenitor cells, for example. In other cases – methods of imaging transplanted cells in humans, for example, or developing microfluidic techniques of cell separation – the exact means by which a new tool or technology is to be produced is uncertain, requiring extensive development before the technology is suitable for widespread use. Thus, contracts for specific tasks will sometimes be the appropriate mechanism; exploratory grants may be more productive in other instances.

CIRM may also wish to set up one or more specialized centers that will develop technology and make it widely available for the broader community – a center for high-throughput screening, for example, or for developing vectors or chips, or for bioinformatics. One example that has been widely discussed is a stem cell bank that would maintain, store and characterize stem cells lines developed in California and elsewhere. A stem cell bank, which would maintain communication and work on a cooperative basis with banks in other states and countries, would operate much like the American Type Culture Collection, storing standardized samples of lines that could be made available to researchers in California and throughout the world. CIRM may also wish to establish information banks that would help investigators find and identify relevant information about stem cell lines.

Finally, CIRM may wish to provide infrastructure that will help investigators through consultation, service or training. For instance, providing expert support for academic investigators who have identified a potential therapy as they navigate the regulatory and other requirements necessary to file an Investigational New Drug (IND) application is one way in which CIRM could facilitate progress in clinical research.

Facilities

An essential component of the infrastructure required to achieve the goals of CIRM will be adequate research space for human embryonic stem cell research. This need has two sources. First, as new stem cell investigators are recruited to non-profit institutions in California to

"There is a crying need for scientists in this field to have research facilities and places to do their work. The hardest problem for people getting into stem cell research is the lack of facilities."

***- Paul Berg,
SPAC Member***

participate in human embryonic stem cell research and as new investigators are trained, new facilities will be required to house them. Second, in many cases, space for research on human embryonic stem cells will need to be separated from space used to carry out NIH-funded research. There is thus an immediate need for space that is dedicated to human embryonic stem cell research in which cell lines that fall outside the federal guidelines can be used. According to Proposition 71, CIRM can use up to 10% of its funds for facilities and capital equipment. CIRM will use this money to build, renovate and equip both large-scale and small-scale facilities for human embryonic stem cell research.

Communities of Science

To encourage communication and collaboration to speed scientific and medical progress, CIRM will engage in a variety of activities whose purpose is to create a vigorous, energetic and committed scientific community of stem cell research in California, including researchers in both non-profit research institutions and in the commercial sector. These activities will include a variety of scientific meetings and workshops of stem cell scientists in California, an annual meeting of CIRM trainees, and other activities.

California has a remarkable concentration of scientific talent, both in the universities, colleges and research institutions and in the biotechnology industry. To achieve its aims, CIRM will need to call on both of these communities and will need to make a special effort to encourage collaboration and communication between them. Thus CIRM scientific meetings will include researchers from both academic and commercial institutions.

In addition to supporting and encouraging scientific relationships within the state, CIRM will facilitate scientific cooperation between California scientists and those in other parts of the United States and abroad. Stem cell research is now being pursued vigorously world-wide, and the California effort, no matter how strong, will be only part of a much larger enterprise. CIRM will need to have programs to encourage exchange of scientific personnel as well as mechanisms that will allow collaborative projects to be pursued between California and non-California scientists. The latter will be particularly important in cases where a key technology or patient population is optimally available outside the state. In these cases, CIRM will actively seek partners for funding outside the state. These could include other governmental funding agencies, private foundations or patient advocacy groups. Many disease-oriented foundations

(e.g. Juvenile Diabetes Research Foundation) have large, well-funded research programs through which partnerships with CIRM might be formed. Because such programs may have access to needed technologies or patient populations outside of California, these partnerships may be particularly useful in leveraging CIRM-funded research.

Responsibility to the Public

Scientific research always takes place in a cultural context; this is especially true for stem cell research, which has been a touchstone for political, legal and ethical controversy, particularly in the United States. CIRM carries out its research with a strong mandate from the California public; accordingly, we have a responsibility to explore the impact of stem cell research on the California public as well as to convey an accurate and unbiased account of the discoveries and potential medical benefits that arise from CIRM research.

***"What should the institute look like? Whatever it looks like, it should involve good, strong, ethical research."
- Interviewee***

First, CIRM has a responsibility to fund scholarly research on ethical and legal matters related to stem cell research and research on the social, economic and health-related impact of stem cell research on society. In so far as possible, such studies should be integrated into the scientific programs rather than separate from it. Such studies need to be well-informed about the science and should also inform the science.

In addition, CIRM should have an active program of education and communication about stem cell research that is directed to the general public. Through our website, through meetings with local groups, through educational materials and through our publications, we will seek to convey accurate and authoritative information about stem cell research and therapies in a comprehensible and accessible way.

California population's is remarkably diverse – a source of its cultural strength and variety. CIRM will strive to reflect that variety in its activities. For complex reasons, the diversity of California is not adequately reflected in the scientific community and CIRM will need to make special efforts to encourage the training and education of minority scientists. CIRM will also need to make special efforts to ensure that clinical trials of therapies resulting from stem cell research include minority populations. Finally, CIRM will make special efforts to maintain communication with its diverse public constituency.

In addition to our responsibility to the general public, CIRM has a special responsibility to patients and patient advocacy groups. They define our purpose and reason for being and it is

important that we maintain strong lines of communication with them, both through our communications activities and as we continue to refine and develop our research program.

Initiatives to Address Needs and Aims

To support its mission and achieve its objectives, CIRM plans to launch a series of scientific initiatives. These initiatives, which are organized according to the categories defined in the "Developing and Enabling Critical Resources" section of the Scientific Strategic Plan, are discussed in detail in the following pages. The following table and figure outline these initiatives and indicates into which of the three broad categories defined in the "Charting the Path to Therapies" section of the plan they are expected to fall.

Initiative	Laying the Foundation	Preparing for the Clinic	Clinical Research
Scientific Training and Development			
Scientist Training / Internships	•	•	•
Technical Staff Training	•		
Scientific Personnel Development	•	•	•
Innovation Science			
hESC Jump Start Initiative	•	•	•
Annual Innovation Grants	•	•	•
Biology of Stem Cells	•		
Egg and Embryo Research	•		
Mission-Directed Science			
New Methods for Development of Stem Cell Lines	•	•	
Stem Cell Based Tissue Engineering in Regenerative Medicine	•	•	
Translational Research	•	•	
Generation and Use of Disease Specific Cell Lines	•	•	
Immune Tolerance	•	•	•
Bio-process Engineering and Automation		•	
Preclinical Product Development		•	
Clinical Investigation			•
CIRM Special Programs			
Disease Teams	•	•	•
Interdisciplinary Research Teams	•	•	•
Tools / Technologies and Infrastructure			
Tools and Technologies	•	•	•
Cores	•	•	
Banks	•	•	
Facilities			
Laboratories / Research Facilities	•	•	
Communities of Science			
Journal / Web Portal	•	•	•
Responsibility to the Public			
Public Outreach	•	•	•
Stem Cell Research and Society: Implications and Impact	•	•	•
Economic Impact	•	•	•

Table 1: Overview of CIRM initiatives

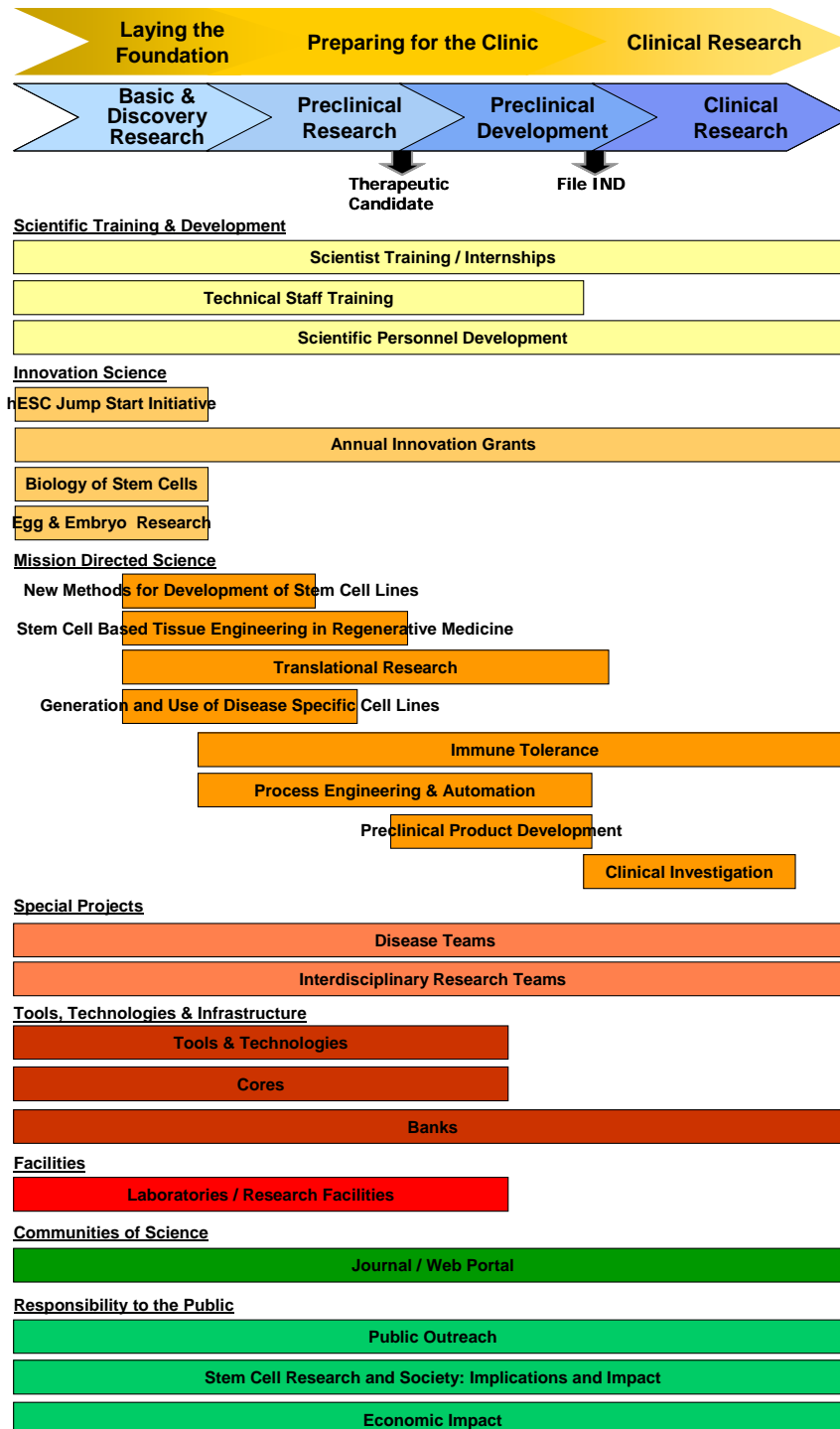


Figure 5: Overview of CIRM initiatives

Specific Initiatives

For each initiative listed below, we describe its significance and objectives, discuss what activities CIRM might pursue under the initiative, and offer a proposed budget estimate. The budget estimate, which is approximate, is based on the number of grants to be awarded, the duration of those grants and the estimated total annual cost (direct and indirect) per grant. The assumptions on which the budget figures are based are given in Appendix D-2.

Scientific Training and Development

Initiative: Scientist Training / Internships

Significance and Objectives

The primary aim of this initiative is to train a cadre of basic and clinical scientists and clinicians needed to expand stem cell research in California. This endeavor will require the scientific training of individuals at all levels to provide a continuing supply of well-trained scientists with the knowledge and skill to lead effective research programs. Training must foster an awareness and appreciation of the critical elements involved in scientific discovery and the subsequent development of research findings into possible clinical therapies or diagnostics. Training must also provide a broad understanding of stem cell research including fundamental biology, knowledge of human diseases, therapeutic development and the social, ethical, and legal issues to promote responsible conduct in research. In addition, CIRM will support specialized training of investigators in new and promising technologies that are likely to emerge.

For example, the knowledge and skills to manipulate human embryonic stem cells have been limited to only a handful of laboratories. It is critically important that this knowledge be expanded to allow more scientists to utilize these cells. CIRM will therefore support specialized courses to train investigators to derive, culture, and maintain human embryonic stem cells in their own laboratories. We see this as an ongoing endeavor that will maintain a cadre of California scientists at the forefront of technical advances in stem cell research.

An important aim of the initiative is to provide training for a wide variety of trainees from scientifically diverse backgrounds, including relevant fields of biology (developmental biology, cell biology, neurobiology, molecular biology, etc.), clinical training programs (medicine, surgery, neurology, cardiology, psychiatry, etc.), bioengineering (tissue engineering, biomedical imaging, etc), as well as ethics and law, where appropriate.

We will encourage institutions to make special efforts, consistent with the law, to recruit and retain individuals from many backgrounds, including under-represented minorities, as trainees and as mentors.

Proposed CIRM Activities

1. A training grant program for pre-doctoral, post-doctoral, and clinical trainees has already been implemented. The aim of this training program is to educate and prepare exceptional trainees for careers in stem cell research through programs developed at institutions with strengths in various areas of basic biology and/or clinical research. Institutions must demonstrate a clear ability and talent to train stem cell scientists. After three years, institutions, both those who have received grants previously and those who have not, will be given the opportunity to enter competition for continuation of this program in order to cultivate successful programs and encourage new ideas.
2. CIRM will support specialized scientist training in the form of courses and workshops in developing and emerging technologies that will enhance and expand the capability stem cell scientists and clinicians. Courses may include, for example, hands-on techniques in the culture and maintenance of human embryonic stem cells or derivation of such cells from blastocysts.
3. A research internship program for undergraduate and master's level trainees will also be created. The aim of this program is to introduce students from diverse educational, ethnic, cultural backgrounds to stem cell research and encourage such students to consider a career in this growing area. Stipends will be provided for undergraduate students to pursue summer research in the laboratories of stem cell scientists.

Estimated Funding Allocations

1. To date, a total of \$38.6 million has been allocated to the training grant program over the next three years, starting in 2006. As an extension of this program, an additional \$13.5 million / year for three years will be committed starting in 2009 and again starting in 2012 (six additional years total). A second training grant program, in which \$4 million / year will be committed for seven years, is expected to begin in 2008, making the grand total to be allocated to training \$147.6 million.
2. CIRM expects to support specialized scientist training in the amount of \$1 million / year from 2009 to 2016, for a grand total of \$8million.
3. An internship program is expected to require an allocation \$200,000 / year for seven year starting in 2008, for a grand total of \$1.4 million.

Total estimated cost - \$157 million

Initiative: Technical Staff Training

Significance and Objectives

In the near future, we expect that California will see a surge in the number of laboratories engaged in stem cell research in both academic institutions and biotechnology or pharmaceutical companies. The growth of this industry will require an educated and well-trained workforce. CIRM will support training of technical staff with essential skills for stem cell research such as cell culture, microscopy, fluorescence-activated cell sorting and analysis, micromanipulation techniques, surgical techniques, and good laboratory practices (GLP). Training will be supported at the undergraduate and masters levels with certificate or degree programs. Successful biotechnology training programs have already been implemented at several California colleges and universities as a means of supporting the broader research community. CIRM will seek to support similar programs that focus efforts towards maintaining an adequate supply of technical staff for stem cell research.

Proposed CIRM Activities

1. CIRM will support technical staff training programs organized and implemented by several California educational institutions that provide coursework and hands-on training in a variety of techniques that are critically important to stem cell research. Training must provide experience and knowledge in the culture and maintenance of stem cells, GLP, basic fluorescence microscopy, and other techniques. Institutions with a demonstrated proficiency in training undergraduate/masters students and faculty with the appropriate knowledge and skill to train such students will be sought.

Estimated Funding Allocations

1. CIRM expects to support technical staff training in the amount of \$5 million / year from 2007 to 2012 and \$2 million / year from 2013 to 2016, for a total of \$38 million.

Total estimated cost - \$38 million

Initiative: Scientific Personnel Development

Significance and Objectives

The future of any field resides in its young practitioners. Although it is an exciting new frontier, young investigators have been discouraged from entering the field of stem cell research because of the restrictions and uncertainty of federal funding. Consequently, there is a dearth of young investigators. It is also generally true that current levels of NIH funding pose special difficulties for investigators in the early stages of their careers. Studies show

that the average age of NIH investigators at the time of their first grant awards has been steadily increasing and is now at 42 for PhD degree holders and 44 for MD and MD / PhD degree holders³.

CIRM seeks to provide special funds for early-stage investigators, both those in laboratories and those doing patient-based research. At the most productive time in their careers, young investigators must deal with financial issues that may threaten to compromise the possibility of doing their best work. Young laboratory investigators are under tremendous pressure to obtain results quickly, thus discouraging them from undertaking high-risk projects. For young medical investigators in clinical departments, the pressure to see patients in order to support their salaries is a major difficulty. CIRM thus proposes a program that would provide both salary and research support for investigators in the early years of their independent careers.

Proposed CIRM Activities

One or more RFAs that would provide research and salary support for young clinical and laboratory investigators in non-profit institutions.

Estimated Funding Allocations

For this program, CIRM expects to support clinical and laboratory investigators each year, at a total estimated cost of \$10 million / year, from year 2007 to 2016.

Total estimated cost - \$100 million

Innovation Science

Initiative: hESC Jump Start Initiative

Significance and Objectives

The first CIRM research grant initiative, Innovation in Human Embryonic Stem Cell Research, is intended to “jump-start” hESC research in California, which was deemed to be the research area of greatest immediate need. This initiative will be carried out through the three programs described below.

³ NIH Office of Extramural Research (http://grants2.nih.gov/grants/new_investigators/resources.htm)

The SEED (Scientific Excellence through Exploration and Development) Grant Program is intended to bring new ideas and new investigators into the field of human embryonic stem cell (hESC) research and will offer an opportunity for investigators to carry out studies that may yield preliminary data or proof-of-principle results that could then be extended to full scale investigations. The goals of the program are: to fund preliminary research in the biology, derivation, and application of hESCs and their derivatives; to fund ground-breaking, exploratory new concepts and approaches in the field; and to attract new investigators - young investigators as well as established scientists in other fields - to direct their focus to hESC research.

The objective of Comprehensive Research Grants Program is to support mature, ongoing studies on hESCs by scientists with a record of accomplishment in this field. This is also an opportunity for investigators with well-developed expertise in hESC research or in a closely-related stem cell field to expand their programs or take promising new directions in hESCs research based on current research. In their application, the Principal Investigator (PI) is expected therefore to provide strong preliminary data to demonstrate feasibility and the promise of the proposed research. PIs may be either senior or junior faculty and must be full-time employees of the grantee organization.

The objectives of the Shared Research Laboratory Grant Program are: to create dedicated laboratory space for the culture of hESCs, including those hESCs which fall outside the federal guidelines, by supporting the creation of core laboratories to be used by multiple investigators and shared by multiple institutions; and to provide an environment (with CIRM-funded space and equipment) for the unrestricted conduct of scientific research on hESCs. A third objective is to offer Stem Cell Techniques Courses within CIRM-funded Shared Research Laboratories to train scientists and technical staff in the growth and maintenance of hESCs by funding hands-on courses teaching hESC culture techniques to be given several times a year for Californian investigators.

Current CIRM activities

1. RFA 06-01: CIRM SEED Grants (Current)
2. RFA 06-02: CIRM Comprehensive Grants (Current)
3. RFA 06-03: CIRM Shared Research Laboratory Grants and Stem Cell Techniques Course (Current)

Estimated Funding Allocations

1. CIRM intends to support up to 30, two-year SEED grants starting in 2007. Each grant will be valued at \$400,000 / year, for a total of \$12 million in both 2007 and 2008, or a grand total of \$24 million.

2. CIRM intends to support up to 25, four-year Comprehensive grants starting in 2007. Each grant will be valued at \$800,000 / year, for a total of \$20 million a year from 2007 to 2010, or a grand total of \$80 million.
3. CIRM intends to provide funding for both shared research laboratory grants (three-year grants for shared laboratory space or for shared laboratory space and for training) from 2007 to 2009 for a grand total of \$31.3 million, not including facilities costs.

Total estimated cost - \$135.3 million (not including \$16.3 million for facilities for shared research laboratory grants)

Initiative: Annual Innovation Grants

Significance and Objectives

In addition to the “jump-start” discussed above, CIRM also anticipates establishing an Annual Innovation Grants Program. These investigator-initiated grants will be awarded annually to individual investigators and to research teams with the twin goals of generating new ideas and advancing existing ones, thereby ensuring that CIRM's activities continue to feed the innovation pipeline. These grants may span the spectrum of basic, translational / preclinical and clinical research.

Proposed CIRM Activities

RFA for Innovation grants.

Estimated Funding Allocation

For this program, CIRM expects to support both individual investigators and research teams. Support for individual investigators will total \$500,000 / year for three years and for research teams will total \$2 million / year per for four years. Awards will start in 2008 and be made annually with the last awards being made in 2014.

Total estimated cost - \$148.5 million

Initiative: Biology of Stem Cells

Significance and Objectives

Stem cells appear to possess great plasticity, but the cellular mechanisms regulating their behavior and fate are not understood. If these mechanisms can be harnessed to obtain

cells specifically required for therapy, diagnosis or drug discovery, it may be possible to restore function to tissues and organ systems that have been compromised by congenital disorders, developmental malfunction, age, injury, disease or drug exposure. An understanding of intrinsic and extrinsic signals, especially those involved in the stem cell niche, and genetic factors that govern the activities of pluripotent cells is crucial in order to utilize them to develop safe and effective treatments for the restoration of function, or to prevent their transformation into tumor-generating cells. Although animal studies suggest that stem or progenitor cells can be derived from a variety of tissues and sources ranging from blastocysts to the adult organism, the requirements and potential for differentiation of each type of pluripotent cell appear to be unique. We lack a clear understanding of the intrinsic properties that distinguish one population from another, and how these populations differ in their response to similar conditions in vitro and in vivo.

It is therefore necessary and important to study the fundamental properties of all classes of human and non-human stem cells, and to confirm, extend, and compare the behavior of stem cells that are derived from different sources or exposed to different regimes. Of high priority are studies to develop methods for identifying, isolating and characterizing specific precursor populations at intermediate stages of differentiation into mature phenotypes, and their relationship to tumor-generating cells. Research efforts on characteristics that distinguish between different types of stem cells and the cellular, molecular and genetic mechanisms that influence their lineage choices are particularly relevant, as are studies that explore the long-term fates of stem cell-derived populations in animal models. Model systems such as the zebrafish, fruit fly, worm and others where functional genomics can be approached easily can contribute in unique ways to our understanding of stem cell behavior.

Proposed CIRM Activities

1. Periodic workshops to review current understanding of stem cell biology, on characteristics that distinguish between different types of stem cells and the cellular, molecular and genetic mechanisms that influence lineage choices, as well as studies that explore the long-term fates of stem cell-derived populations in animal models.
2. An RFA to support projects that address the fundamental biology of stem cells and make comparisons between different classes of human stem cells and between human and non-human stem cells.

Estimated Funding Allocations

1. CIRM estimates the costs of the three proposed workshops at \$100,000 each.
2. CIRM intends to support three-year grants for activities related to the fundamental biology of stem cells. One round of grants will be released in 2008 and a second in 2011, for up to \$12.5 million a year from 2008 to 2013, or a total of \$75 million.

Total estimated cost - \$75.3 million

Initiative: Egg and Embryo Research

Significance and Objectives

Much of the information about early human development comes from studies of embryogenesis in other species such as the mouse. Despite similarities, development in mice differs from human development in many important respects. For example, embryonic and fetal development in mice takes 18 to 20 days; in humans, the process takes nine months. In the past two decades, important information about early human embryogenesis has come from efforts to improve the success rates for in vitro fertilization (IVF). These efforts have taken place largely in other countries where clinics and research institutes have developed *in vitro* conditions that allow the investigation of fertilization and blastocyst formation. Few of these studies have been conducted in the US due to passage of the Dickey Amendment in 1995, which prohibits the use of federal funds for the creation of human embryos for research purposes, or for research in which human embryos are destroyed, discarded, or knowingly subjected to risk of injury or death. The Dickey Amendment prohibits studies on human egg development beyond fertilization and prohibits federally funded scientists from attempting Somatic Cell Nuclear Transfer (SCNT) to derive stem cell lines that model human disease. Such studies have an immediate, compelling medical rationale, and are critical to the progress of stem cell research, yet they cannot be pursued with federal grants.

CIRM encourages scientific research aimed at expanding fundamental knowledge of processes that underlie human egg and embryo development. Scientists are encouraged to lead the way in determining the genes, factors and their mechanisms of action involved in regulation of human embryonic development. In addition, CIRM encourages research into epigenetic mechanisms critical to the development of the human egg and embryo, including areas such as the establishment and maintenance of methylation patterns or imprinted loci in the early embryo; the timing, mechanisms and role of genomic methylation in gametogenesis; and the reproductive determinants and consequences of X-chromosome inactivation.

Of particular interest is finding new ways to generate human eggs that can then be used for SCNT. Recent studies suggest several novel possibilities. Although it is now well established that fetal mammalian eggs originate from somatic stem cells, some reports indicate that germ cells and gametes (sperm and eggs) can be derived from embryonic stem cells. Other studies show that human eggs can develop in vitro from ovarian surface epithelium cells derived from human ovaries and cultured in the presence of an estrogen-containing medium. The oocytes cultured in this way appeared viable and went on to successfully complete the first meiotic division to become mature human eggs. If these or other innovative methods can be employed successfully to generate human eggs suitable for SCNT, this would obviate the necessity of putting egg donors at risk for discomfort and potential harm in order to acquire the precious eggs needed.

Proposed CIRM Activities

1. Workshop to review the current state of the science of human egg development and early embryogenesis, and to identify the needs in the field. The workshop will also review the success of new methods to generate eggs ex vivo or in vitro and the challenges faced by investigators in this endeavor.
2. An initiative to support research to determine mechanisms underlying early human development. Of interest are studies to examine the events involved in cell division, cell migrations, establishment of pattern, interactions between cells and between cells and extracellular materials, fate determination and differentiation. The program includes models of human disease, genetic regulation of diverse fundamental cellular processes, epigenetic and genomic regulation of gene expression, genetic networks and mutations, developmental signaling, and genetic maps.
3. An RFA to stimulate research on developing novel methods to generate human oocytes suitable for SCNT.

Estimated Funding Allocations

1. CIRM estimates the costs of the two proposed workshops at \$100,000 each.
2. CIRM intends to support three-year grants for research related to early human development starting in 2008. One round of grants will be released in 2008, for a total of \$2.5 million a year from 2008 to 2010, or a total of \$7.5 million.
3. CIRM intends to support four-year grants for research related to novel methods to generate human oocytes. One round of grants will be released in 2008, for a total of \$2.5 million a year from 2008 to 2011, or a total of \$10 million.

Total estimated cost - \$17.7 million

Mission-Directed Science

Initiative: New Methods for Development of Stem Cell Lines

Significance and Objectives

Pluripotent stem cells are capable of self-renewal and have the developmental potential of differentiation into all three germ layers - ectoderm, mesoderm and endoderm. Because

such cell populations have the potential of generating all the cell types in an organism, they play a key role in regenerative medicine and in cell replacement therapies.

To date, two types of pluripotent human stem cells have been generated successfully – human embryonic stem cells (hESCs) from blastocysts and human embryonic germ cells from the fetal germinal ridge. A variety of alternative methods have been proposed, many involving reprogramming of adult somatic cells or of their nuclei. Some of these have been successfully used in non-human species (e.g. somatic cell nuclear transfer); others, while promising, are still “works in progress” (e.g. the creation of “cybrids” through fusion of a somatic cell with an ES cell, and selective overexpression of critical transcription factors). Several other ideas are still in the hypothesis stage. These include identifying factors such as those highly expressed within the cytoplasm of oocytes that can directly regulate or reset the developmental program of adult somatic cells. Finally, there are numerous efforts to find and to document the presence of pluripotent stem cells harvested from adult tissues. Although many of the early observations of such “transdifferentiation” from one lineage to another can be attributed, on closer examination, to cell fusion, a few careful studies are promising and deserve verification or confirmation (e.g. the identification of multipotent adult progenitor cells or MAPCs from bone marrow and cells with MAPC-like qualities in umbilical cord blood).

Pluripotent stem cells derived from new sources such as adult tissues will enable investigators to generate disease-specific and genotype-specific cells of many phenotypes. Such cells have great value for drug discovery and understanding specific disease mechanisms. In addition, studies on reprogramming of adult human nuclei and on how reprogramming occurs will provide important insights on many aspects of early human development as well as how the process of differentiation keeps mature cells in the adult state. Importantly, methods that will not require the donation or use of either human embryos or eggs will reduce significantly the moral and ethical concerns that surround methods that are currently in use. Finally, new methods of producing pluripotent stem cells will be particularly important because it may be difficult to obtain excess embryos from many racial groups. These new techniques will enable the generation of a wide spectrum of cell lines that will represent many HLA types and serve the genetically diverse populations on the planet.

Proposed CIRM Activities

1. A biennial workshop on current status of alternative methods of generating pluripotent human stem cells and their utility and ability to fulfill FDA regulations for use in cell replacement therapies.
2. An RFA to support the discovery and implementation of alternative methods of generating pluripotent human stem cells.

Estimated Funding Allocations

1. CIRM estimates the costs of the three proposed workshops at \$100,000 each.
2. CIRM intends to support three-year grants for research related to the discovery and implementation of alternative methods of generating pluripotent stem cells. One round of grants will be released in 2008, for a total of \$4 million a year from 2008 to 2010, or a grand total of \$12 million.

Total estimated cost - \$12.3 million

Initiative: Stem Cell Based Tissue Engineering in Regenerative Medicine

Significance and Objectives

A large number of Americans suffer organ and tissue loss every year from accidents, birth defects, hereditary disorders and diseases. Stem cell-based tissue engineering is an avenue of interdisciplinary scientific inquiry that can lead to new approaches for treating dysfunctions in many human organ systems. This effort depends on integrating discoveries from stem cell biology, biochemistry, material science and biomedical engineering; the overall objective is to engineer functional tissues *in vitro* for implantation *in vivo* with the purpose of replacing, repairing, or preserving, organ function or for use as 3D tissue model systems for drug development. The therapeutic use of bioengineered tissues hinges however on the ability of such implanted materials to thrive, integrate and function in a biologically meaningful manner *in vivo* without causing adverse effects.

In tissue engineering, the material components, usually called matrices or scaffolds, serve to direct the growth of cells migrating from surrounding tissue or of cells seeded within these porous structures themselves. They provide a suitable substrate for cell attachment, proliferation, differentiated function, and cell migration. Although much remains to be known regarding optimal materials for, and design of, successful implanted matrices and scaffolds, it is equally important to understand how they interact with their biological surroundings.

In stem cell research, great progress is being made in our understanding of the specific requirements of stem cells to proliferate and differentiate along specified lineages through careful studies in culture. Unfortunately, the behavior of cells *in vitro* does not adequately predict how these same cells will behave when transplanted into the living host where multiple known and unknown factors converge to influence the biological process. We need to know the whole spectrum of factors present *in vivo* that influence the fate of implanted cells and engineered tissues. Therefore the next stage in developing cell and tissue

restoration therapy requires understanding how the newly generated cells and tissues will behave within the host.

Recent reports indicate that the "niche" or local microenvironment that a stem cell encounters governs its behavior and fate. For example, adult neural stem cells produce neurons when transplanted into the neurogenic zone of the hippocampus, but produce astrocytes in the environment of the spinal cord. In addition to regional differences, the microenvironment encountered by a stem cell may vary as a function of age of the host organism. Similarly, alteration of the niche by injury, drugs or other circumstances is likely to affect the ability of transplanted stem cells and engineered tissues to survive, differentiate and integrate into existing structure of the host. Understanding these changes will be important in making decisions about the use of cell replacement therapies in very young or elderly patients, in patients with a history of alcohol or drug usage, or suffering from injury or other conditions.

Transplanted cells and materials also can act to influence and change host cells in their vicinity. Stem cells may release agents that alter the activity or resiliency of damaged host cells. These dynamic interactions are inevitable as living cells and tissue contact, react and respond to each other in time and space. Teasing out and understanding these interactions pose a major challenge that must be faced in order to develop realistic cell replacement therapies and enhance normal tissue regeneration.

To address these needs, CIRM supports interdisciplinary research in tissue engineering that integrates the use of stem and progenitor cell populations with defined matrices and scaffold materials with the goal of developing novel structures for restoration of function. In addition, CIRM encourages studies that establish and identify the nature and action of microenvironmental cues that influence the integration and behavior of transplanted cells and tissues. This initiative targets cellular, molecular and genetic mechanisms that act *in vivo* to influence stem and progenitor cell survival, homing/migration, adhesion, differentiation, plasticity and tumorigenicity. Areas of research interest also include evaluation of the effects of external factors such as stress and exercise on the microenvironment within the host organism, and how these changes in microenvironment influence the behavior of stem cells at different periods throughout the lifespan of the organism; and development of assays facilitating the discovery of novel endogenous signals that modulate stem cell behavior and fate, as well as signals generated by stem cells that regulate components of the local host tissue.

Proposed CIRM Activities

1. Bi-annual workshops to review the state of the field and new developments in stem cell-based tissue engineering and on the role of the niche in regulating the fate and function of grafted cells and tissues.

2. An RFA to support interdisciplinary projects that target the use of stem cells and their derivatives in tissue engineering.
3. An RFA to stimulate studies on interactions between grafted stem cells and/or their derivatives and the microenvironment or niche within the host with the goal of designing and optimizing cell replacement therapies.

Estimated Funding Allocations

1. CIRM estimates the costs of the four proposed workshops at \$100,000 each.
2. CIRM intends to support five-year grants, focused on interdisciplinary projects in this area. A round of grants will be released in 2008 and additional rounds will occur in years 2010 and 2012. Annual funding for a given round of grants will be up to \$5MM, for a total funding of \$75 million.
3. CIRM intends to support three-year grants, focused on the microenvironment for grafted cells. One round of grants will be released in 2008 and second in 2011, for a total of \$2 million a year from 2008 to 2013, or a total of \$12 million.

Total estimated cost - \$87.4 million

Initiative: Translational Research

Significance and Objectives

New opportunities for preventing and treating disease arise from breakthroughs in basic research. Discoveries across a broad range of research in stem cell biology will offer new concepts, models and even molecules for the treatment of injury and disease. As part of its mission to develop therapies and cures, CIRM is committed to encouraging the "translation" of these discoveries into new treatments. The goal of this initiative is to implement a program of grants that will support milestone-driven projects focused on the identification and pre-clinical testing of new therapeutics. The program will facilitate the effective review and research administration of translational research projects and will accelerate the translation of discoveries in basic stem cell research to treatment in the clinic.

Emerging strategies for therapy may include: cell replacement and regenerative therapies that repair the damaged tissues and restore function; therapies based on harnessing natural endogenous factors and molecules that promote survival, growth and repair of susceptible cells; protective agents that fend off the insidious destruction of cells and tissues; therapies that silence or replace defective genes; and interventions that encourage the "plasticity" of the cells and tissues in the body to compensate for damage. To generate opportunities such as these and bring them to fruition, CIRM plans to support a wide spectrum of research

to discover candidate therapeutics, to test them in relevant in- vitro and in vivo models to discover mechanism and demonstrate preclinical proof of principle. For the most promising candidates, CIRM plans to support the preclinical development studies which will allow clinical studies in humans. These studies include the rigorous animal safety testing required prior to testing in humans including the testing of side-effects that may arise from cell replacement use of stem cell derivatives, such as the risk of tumorigenicity.

Efficient preclinical tests can identify and ensure that the most promising potential therapies proceed rapidly to clinical testing. Furthermore, good preclinical data is essential so that researchers can predict which treatments and doses are most useful and which patients might benefit. New biomarkers, innovative approaches to testing, and reliable outcome assessments are essential to this process.

Proposed CIRM Activities

1. Workshops to review current approaches that use disease-specific pluripotent stem cells and their derivatives to understand the bases and progression of diseases, and/or to test or screen for toxicity and/or drugs that could prevent, cure, delay or reverse progression of disease.
2. An open RFA to support the translation of promising discoveries from stem cell research to target the treatment of an identified target disease or injury with the goal of generating an IND at the end of the process. This RFA would have two stages.
 - a. Stage 1 would support research that seeks to discover a therapeutic (diagnostic) candidate.
 - b. Stage 2, or preclinical development, assumes that a candidate therapeutic has been discovered, that convincing proof of principle has been demonstrated in preclinical models and that there is good rationale for proceeding to studies in humans. Preclinical development, to be successful, requires the interaction of people with different areas of expertise including clinicians, biologists, toxicologists and bioengineers. CIRM will strongly encourage, if not require collaboration, in the preclinical programs that it funds. CIRM recognizes a responsibility in choosing the programs that it will fund for preclinical development funding given this is the penultimate stage prior to submitting an application to the FDA for testing in humans. CIRM will ensure that it receives appropriate expert advice from persons with the requisite scientific, preclinical, process and clinical expertise prior to funding stage 2 programs.

Estimated Funding Allocations

1. CIRM intends to support three-year grants for Stage I activities. One round of grants will be released in 2007 with total annual funding of up to \$20MM. Additional rounds

of funding will be in 2010 and 2013 with total annual funding of up to \$40 MM, for a total of \$300 million.

2. CIRM intends to support three-year grants for Stage 2 activities. Rounds of grants will be released in 2009, 2010, 2012, 2013, 2015 and 2016, for an annual funding per round of up to \$9MM or a total of \$162 million.

Total estimated cost - \$462.6 million

Initiative: Generation and Use of Disease Specific Cell Lines

Significance and Objectives

Human stem cells could be important tools in developing therapies, including ones based on cell replacement, for diseases for which there are no current treatments. There are, however, other important applications for such cells: to serve as cell-based models of diseases, to investigate the molecular bases of diseases, and to function as tools for drug discovery to treat these diseases. The most effective way to acquire these cellular models is through the generation and use of disease-specific human embryonic stem cells (hESCs). For example, with disease-specific cell lines in hand, it will be possible to trigger their differentiation into specific mature phenotypes with which to study the disease process, or even dissect the molecular processes leading to the symptoms and progression of the disease.

Current methods to produce hESCs start with *in vitro* fertilization followed by extraction of the inner cell mass from the blastocyst; hESCs are derived from cells of the inner cell mass. The genetic background of cell lines acquired by these methods is determined by the donors of the embryos used for their generation. To develop cellular models of heritable disease, it is necessary to derive hESC lines with the genetic background(s) at risk for disease or that would lead to disease. A number of technologies exist to achieve this goal for diseases where the gene responsible has been identified. For example, it is theoretically possible to introduce the responsible mutation or genetic defect into existing hESC lines by homologous recombination. A second method is to produce hESC lines from embryos that have been identified, through pre-implantation genetic diagnosis (PGD) as bearing known disease genes. Such embryos are not selected for implantation and may be donated for research.

Both approaches require knowledge of the exact mutation that causes a disease condition. Unfortunately, we do not as yet know the genetics underlying most inherited diseases, so these approaches, while powerful, have limited utility. A potential solution to this problem is Somatic Cell Nuclear Transfer - a technology that could, in theory lead to the generation of disease-specific and patient-specific hESCs. The feasibility of this important technology has

been demonstrated in a variety of animal studies, but not as yet with human cells. Other innovative techniques may involve reprogramming of adult cells and nuclei to produce human pluripotent stem cell lines. Pluripotent stem cells derived from new sources such as adult tissues may enable investigators to generate disease-specific and genotype-specific, cells of many phenotypes. Importantly, methods that will not require the use of either human embryos or eggs will reduce significantly the moral and ethical concerns that surround methods that are currently in use.

Proposed CIRM Activities

1. Workshop every other year to review current approaches that use disease-specific pluripotent stem cells and their derivatives to understand the basis and progression of diseases, and/or to test or screen for toxicity and/or drugs that could prevent, cure, delay or reverse progression of disease.
2. RFA to support the generation of pluripotent, disease-specific stem cell lines and their use for the development of treatments for these diseases.

Estimated Funding Allocations

1. CIRM estimates the costs of the four proposed workshops at \$100,000 each.
2. CIRM intends to support three-year grants for the generation of pluripotent, disease-specific stem cell lines. One round of grants will be released in 2008 and one round in 2011, with annual funding of up to \$5 million for a total of up to \$30 million.

Total estimated cost - \$30.4 million

Initiative: Immune Tolerance

Significance and Objectives

An important potential problem for transplantation of allogeneic stem cell derivatives is rejection of the transplant by the recipient's immune system. Currently, patients receiving tissue transplants are treated chronically with immunosuppressive drugs that render them vulnerable to infection, malignancies and drug-specific toxicity. For transplant recipients, these unwanted consequences result in a 5-10% increase in mortality. Techniques for inducing robust, sustained, tolerance of allogeneic transplants would therefore be of major benefit, not only for stem cell replacement therapies, but for other transplant therapies, such as solid organ transplants.

Immune tolerance for recipients of solid organ transplants can be achieved by concurrent bone marrow transplantation from the same donor. This approach is successful in the

absence of immunosuppression, as has been shown in rodents, and in two cases, in humans. The cells in the bone marrow transplant that are responsible for engraftment of the immune system adult hematopoietic stem cells (HSCs). Unfortunately, the numbers of HSCs that can be obtained is relatively small. Reliable and safe mechanisms of expanding their numbers could lead to routine use of engraftment of the immune system as a mechanism of inducing tolerance. If successful, this technology would prove useful for treatment of blood and immune disorders, for solid organ transplantation and for treatment of autoimmune disease. The availability of a source of purified HSCs for bone marrow transplantation would also avoid the problems of graft-versus-host-disease (GVHD), the major complication of bone marrow transplantation. Alternatively, methods to improve their engraftment and repopulation in vivo could improve the efficiency of engraftment.

CIRM seeks to fund an initiative that would explore mechanisms for producing large numbers of HSCs either by inducing the *ex vivo* expansion of cells derived from bone marrow or umbilical cord blood, or by deriving them from embryonic stem cell lines. Investigation of methods for improving engraftment will also be of interest. Improved ability to reconstruct the immune system using any of these or other methods would presumably be tested in mouse or other animal models, before initiating human studies.

Proposed CIRM Activities

1. Workshop to review the feasibility of various approaches.
2. Initial RFA to support research on in vitro and animal systems.
3. If successful, later RFAs to test the results in humans.

Estimated Funding Allocations

1. CIRM estimates the costs of the four proposed workshops at \$100,000 each.
2. CIRM intends to support three-year grants for preliminary research on in vitro and animal systems. One round of grants to be released in 2008 and one round in 2011; annual funding for each round will be up to \$2.5 million for a total of \$15 million.
3. CIRM intends to support three-year grants for continuing research on in vitro and animal systems. One round of grants to be released in 2011 and one round in 2014; annual funding for each round will be up to \$7.5 million, for a grand total of \$45 million.

Total estimated cost - \$60.4 million

Initiative: Bio-Process Engineering and Automation

Significance and Objectives

Stem cells offer the promise of regenerative cellular therapies for replacing defective, damaged or missing cell functions. These cellular therapies are likely to be complex products; they may be differentiated from an autologous stem cell line derived, for example, from somatic cell nuclear transfer; or, alternatively, derived from a stem cell line from an unrelated donor. In addition, such stem cell based cell therapies may be encapsulated or be part of a scaffold. These types of therapies offer particular challenges for production. They must meet the standards of product consistency and safety required by the FDA and by patients and they must also be cost effective to enable as broad a usage as is appropriate. Such complex cell therapy products require efficient processes to deliver a consistent product. Automated and semi-automated systems, including computer based bio-processing and robotics may ultimately provide the solution to delivery of a consistent, cost effective cell therapy product, even individualized cell therapy products. For example, somatic cell nuclear transfer, were it to become a source of autologous cell lines, will likely require robot assisted manipulation if it is to be efficiently and effectively accomplished. The manual procedure demands a high level of technical skill and is likely to be difficult even once shown to be possible.

Stem cell lines, or the differentiated lines derived from them, could benefit from optimization of expansion and differentiation conditions by automated or semi-automated systems that conduct multi-parameter tests of variables. Similarly, once optimal conditions are determined, semi-automated or automated systems could ensure the consistent production of a given product.

CIRM recognizes that being able to bring cell therapies to patients who would benefit from such therapies requires the development of efficient semi-automated and automated bio-processing systems that will include sophisticated software and robotics. CIRM intends to support research and development in the area of automated and semi-automated bioprocess engineering for cell therapies based on stem cells. CIRM would encourage collaboration among experts in disciplines such as bioengineering, process engineering, stem cell science and computer science and between the non-profit and for-profit sectors.

Proposed CIRM Activities

1. RFA open to academic and for-profit institutions to support research and development of semi-automated and automated bioprocess systems to enable the efficient and effective development of cell therapies that meet regulatory requirements and patients' expectation for a safe and consistent product at a reasonable cost

Estimated Funding Allocations

1. CIRM intends to award three-year grants for research and development of semi-automated and automated bioprocess systems. One round of grants will be released in 2009 and one round in 2012; annual funding will be up to \$10 million.

Total estimated cost - \$60 million

Initiative: Preclinical Product Development

Significance and Objectives

Preclinical development includes activities that are ultimately directed towards ensuring that a new drug or biologic (a cell therapy is a type of biologic) that is to be used in research in humans is safe and affords potential benefit. Testing in humans is highly regulated; in the US, the FDA is the primary regulatory authority. This is also the stage, along with earlier preclinical research, where studies can be conducted that lead to the underlying understanding of the molecular, cellular and whole organism basis of the effect of treatment on disease or injury. Preclinical development involves optimizing conditions for therapeutic activity (e.g. dose, delivery) and conducting pharmacokinetic and pharmacodynamic (PK/PD) studies in preclinical animal models. PK studies address what the organism does to the therapeutic agent; PD studies address what the agent does to the organism. Preclinical development includes defining the potential of the biologic/drug for harm by rigorous testing in several animal species to determine the conditions for and the types of harm that could result from treatment. To meet Investigational New Drug (IND) requirements, preclinical safety studies are required to be conducted under Good Laboratory Practice (GLP) standards to ensure the quality and the integrity of the data derived from the testing. Preclinical development also includes developing the conditions for scalable production of the biologic/drug and producing it under conditions that allow for lot to lot consistency in identity, purity and potency. Typically, the biologic/drug for IND-enabling safety studies is produced in the same way as the material is produced that is intended for use in humans, that is under GMP (Good Manufacturing Practices). Preclinical development includes developing and/or performing the assays for bioactivity; for purity, potency and identity; and includes testing for stability. Finally, preclinical development includes clinical protocol design as this is a crucial element in defining the type of preclinical PK/PD and safety studies necessary prior to conducting clinical research in people. Preclinical development may take from 1-3 years, the industry average is 1.5 years for a typical small molecule drug or therapeutic protein (M. Dickson and Gagnon, J.P. Nature Rev Drug Disc. 3: 417-429, 2004); given the limited experience with stem cell derived cell therapies, the longer time is likely to be the better estimate.

CIRM believes that preclinical development is a critical gap, or “valley of death”, for both academia and industry in moving forward very novel therapies, such as stem cell-derived

cell therapies. CIRM intends to support preclinical development activities; directly, through providing funding to investigators in academia and industry to conduct the necessary activities and indirectly, through core service and facilities such as regulatory/protocol development services and GMP production. Preclinical development, to be successful, requires the interaction of people with different areas of expertise including clinicians, biologists, toxicologists and bioengineers. CIRM will strongly encourage, if not require collaboration, in the preclinical programs that it funds. CIRM recognizes a responsibility in choosing the programs that it will recommend for preclinical development funding given this is the penultimate stage prior to submitting an application to the FDA for testing in humans. The group that reviews preclinical development proposals and recommends proposals for funding to the ICOC will include representatives with the requisite scientific, preclinical, process and clinical expertise as well as patient advocates.

The objectives for this initiative are as follows:

- Support preclinical development of novel stem cell or stem cell derived cures, therapies, and diagnostics that can enable safe testing in people of novel therapies and/or diagnostics.
- Promote multi-disciplinary input and participation to ensure a reasonable preclinical plan and a justification for proposed studies in the context of that plan.
- Encourage leverage of funding

Proposed CIRM Activities

1. RFA(s) open to non-profit and for-profit entities for the conduct of studies and activities with novel stem cell or stem cell-derived candidates required prior to clinical research. Such activities may include in the case of a cell therapy:
 - a. Preparation of Master and Working cell banks
 - b. Development of scalable processes for cell production and purification
 - c. Production of GLP cell product and GMP cell product
 - d. Development and/or performance of assays to assess purity, potency and identity
 - e. Determination of long term cell stability
 - f. Conduct of IND supporting pharmacology and PK/PD studies (activity, dose, homing, maintenance of function)
 - g. Conduct of IND supporting safety studies (tumorigenicity, toxicity)
 - h. Development of clinical protocol

Analogous activities for a stem cell derived small molecule drug or biologic (other than cell therapy) may also be considered for funding.

The proposed studies must be in the context of a focused and coherent preclinical plan developed with input from appropriate experts and targeted towards a regulatory filing for approval to test in humans. Collaboration will be strongly encouraged and may be required as relevant. Collaborations between academic and industry scientists are encouraged. Institutional or other organizational support is encouraged but not required. Proposals will be for up to 3 years. Continuation of funding during the period will be contingent upon achievement of mutually agreed to milestones

Estimated Funding Allocations

1. CIRM intends to award three-year grants. Rounds of grants will be released in 2008, 2010, 2012, and 2014; annual funding per round is up to \$9 million.

Total estimated cost - \$108 million

Initiative: Clinical Investigation

Significance and Objectives

The development of novel therapeutic or diagnostic approaches based on stem cells for the treatment of patients with severe injury or degenerative disease ultimately relies on clinical research conducted with human subjects. This area of patient –oriented research includes the testing of new technologies (e.g. for the delivery of cells); testing to refine the use of or evaluation of the therapy for patient benefit (e.g. mechanistic testing to provide surrogate measures of benefit) and the clinical trials focused on developing a commercial product.

It is the academic physician-scientists at academic medical centers and the small companies who are at the forefront of clinical research for novel therapeutic approaches such as stem cell derived therapies. Despite the importance and necessity for clinical research, funding of such research is a key challenge both for investigator-initiated clinical research by a physician-scientist in the academic medical setting and for the small company seeking to develop innovative therapies. Academic clinical research faces funding challenges due to: diminished ability of clinical departments to underwrite research based on patient care revenues; a decline in share of industry-sponsored clinical trials; a flat or declining NIH budget over the near term; burdensome regulatory requirements and undervaluation by the academic medical center. Similarly, small companies who are developing stem cell therapies face funding challenges as normal sources of funding through venture capital investment or partnerships with the bio-pharmaceutical industry are

unlikely to be available to support early clinical development for very novel therapeutic approaches. The ability to carry out clinical research will lead to the advances that enable successes in early clinical development (e.g. Phase I safety studies and in some cases, Phase II clinical proof of principle). It are these successes that can act as the catalyst to spur industry and investment interest leading to further development and commercialization of promising new therapies to benefit patients.

CIRM intends to contribute to the support of early stage clinical research in order to bring promising therapies and diagnostics based on stem cell research to a stage where public and private sector investment would be available. CIRM does not intend to support pivotal Phase III studies. These studies typically involve a large number of patients and are therefore expensive. They are also critical for defining what will be the approved use for a novel therapy/diagnostic and therefore best designed and conducted by the commercializing organization. Similarly, a novel biologic therapy can be more rapidly made available to patients if the therapeutic agent used in the pivotal study (studies) is produced using the intended commercial production process. Again, the commercializing organization is most vested in and therefore best suited to make commercial production decisions. The for-profit sector is best positioned to commercialize therapies and diagnostics for patient use and should be able to provide and/or attract the requisite funding for pivotal trial, registration and commercialization.

Clinical research, especially early clinical research, benefits from multidisciplinary input from and participation of biologists, preclinical and process scientists as well as clinicians. CIRM strongly encourages and may require such multidisciplinary participation.

CIRM recognizes a responsibility to ensure that the clinical research it funds is scientifically and medically sound and does not pose an undue threat to patients who participate in clinical research studies. To this end, CIRM, for the review of clinical research proposals, will ensure that the review panel includes appropriate scientific, preclinical, process, statistical and clinical expertise in addition to patient advocates.

The objectives for this initiative are as follows

- Support clinical research on novel stem cell or stem cell derived cures, therapies, diagnostics and technologies that can enable the ultimate commercial development of cures, therapies, and diagnostics that benefit patients.
- Support both academic investigator-initiated and industry initiated clinical research in recognition of the important contributions that both can make in clinical research of stem cell and stem cell derived cures, therapies and diagnostics.
- Promote collaboration especially between industry and academia
- Leverage funding

Proposed CIRM Activities

1. RFA for the conduct of goal-oriented clinical research with new or novel stem cell or stem cell-derived candidates to refine the use of or evaluation of candidate therapies (diagnostics) or to test novel therapeutic approaches. Proposals may range from studies that focus on understanding disease in humans and developing biomarkers or measures for disease to research supporting experimental new therapies for the treatment of disease or injury. Proposals will be for up to 4 years; continuation of funding over duration of the grant will be contingent upon the achievement of mutually agreed upon milestones. Funding could cover clinical biologic (drug) supply; protocol design and implementation; supporting complementary non-clinical studies; analytical services and data management and analysis. Institutional or other organizational support is encouraged but not a requirement. Collaboration, especially between clinical and basic or translational research scientists or other interdisciplinary scientists, if relevant, is required
2. RFA for the conduct of clinical trials with novel stem cell or stem cell -derived candidates with the goal of product registration. Clinical trials eligible for funding are those requiring regulatory approval that are designed to evaluate safety (Phase 1) or that provide proof of concept (Phase 2). Funding could cover clinical biologic (drug) supply; protocol design and implementation; supporting complementary non-clinical studies; analytical services and data management and analysis. Collaboration between for-profit and academic investigators is strongly encouraged. The criteria for funding recommendation will include, among others, defined medical need, a potential new solution and a reasonable expectation that the innovation will be further developed by the market (therapy is competitive). Matching funds will be required. Funding is staged and contingent upon successful meeting of milestones.

Estimated Funding Allocations

1. CIRM intends to award a series of three-year grants for goal-oriented clinical research. Each grant will be valued at \$2.5 million / year. Grants will first be awarded in 2009, with additional grants will be awarded in 2010 and again in each of years 2011, 2012, 2013, 2014 and 2015, for a grand total of \$277.5 million.
2. CIRM intends to award a series of grants for clinical research with the goal of product registration. Each Phase I grant will last two years and be valued at up to \$5 million and each Phase II grant will last three years and be valued at up to \$10.5 million. CIRM anticipates awarding Phase I and Phase II grants totaling f \$173.5 million.

Total estimated cost - \$451 million

CIRM Special Programs

Initiative: Disease Teams

Significance and Objectives

The intent of this initiative is to explore a new method of integrating and organizing the highest quality basic, translational and clinical research with the specific aim of producing a therapy for a particular disease or group of diseases whose research is poised for the development of therapies. The rationale for the initiative is the idea that development can proceed faster, more efficiently and more effectively when: a) there is a comprehensive plan for development, leading from the laboratory to the clinic; b) the multidisciplinary members of the team necessary to implement the plan participate in all of its phases and c) there is active team management.

The initiative will call for the formation of a team that brings together the necessary basic, translational and clinical scientists, who will work together over a period of years to develop a therapy based on stem cell research for one or more related diseases or disorders. Team members need not be confined to a particular institution or company, but should consist of the best people in California for the particular purpose. If funding is available from other sources for out-of-state activities, the team may also include individuals from outside the state of California. Teams may also include individuals from both non-profit and commercial institutions as members. To facilitate collaboration, CIRM will also provide funds for enhancing communication among team members through meetings and telecommunications.

The intent of this initiative is not to fund open-ended research for an extended period, but to fund work that follows a careful, detailed and plausible strategy with defined milestones for bringing a therapy to clinic. The project will be expected to have a comprehensive plan, including specific goals with a road map and timeline for achieving the goals. Each phase of the work to be done should be clearly described within the plan, with the activities of relevant personnel described, along with specific objectives and milestones for each phase of the work. A key aspect of the initiative will be the insistence by CIRM on strong management of the project. The disease team will be strongly encouraged to include a professional manager with experience in project management in the area of therapeutic development during the discovery and preclinical research phases of the project but will be required to have such expertise in place during preclinical development and clinical investigation. Progress and overall strategy will be closely and regularly evaluated by a group that includes the manager, key scientific personnel, outside experts and CIRM staff.

The circumstances and stage of development vary for research on different diseases, so that at any given time, some diseases may have potential therapies that are ready for development in a strongly coordinated and directed way, whereas others may not yet be at that stage. Therefore, building a disease team may be more suitable at a particular time, for some diseases more than others. The applicants must make the case that this approach will be feasible and advantageous for the particular disease or disorder that they propose, and that the expertise and resources are available in California (or elsewhere, for a cooperatively-funded project) to make this approach succeed.

Initially, CIRM plans to fund a small number (2-3) of such projects on an experimental basis, with the possibility of funding more projects in the future. Because of the complexity of the project, CIRM will initially offer an RFA for a planning grant to support the preparation of an application for developing a disease team targeting specific therapies.

Proposed CIRM Activities

1. Workshop to discuss the concept, implementation, management and review of disease team grants.
2. RFA for planning grants
3. Initial RFA for disease teams
4. Later RFAs for planning grants and disease teams.

Estimated Funding Allocations

1. CIRM estimates the costs of the two proposed workshops at \$100,000 each.
2. CIRM intends to support a series of \$100,000 planning grants, each to last one year. Grants will be awarded in 2007, 2008, and 2010, for a grand total of \$1.8 million in awards.
3. CIRM intends to support a series of grants for disease teams, with each grant to total up to \$20 million over eight years. Grants will be awarded in 2008, 2009, and 2010, for a grand total of \$120 million.

Total estimated cost - \$122 million

Initiative: Interdisciplinary Research Teams

Significance and Objectives

This initiative will explore a new method of integrating and organizing a group of investigators who will work together towards a specific, highly focused goal. We particularly encourage multidisciplinary teams and/or teams formed between investigators in non-profit institutions and in the private sector. The rationale for the initiative is the idea that for certain types of projects, progress will be faster and more efficient when: a) there is a specific goal and a plan of work with a timeline and milestones; and b) the multidisciplinary members of the team plan participate in all of its phases.

The initiative will call for the formation of a team that brings together the necessary skills to achieve the selected goal, including biologists, engineers, computational biologists or others as needed. Team members need not be confined to a particular institution or company, but should consist of the best people in California for the particular purpose. If funding is available from other sources for out-of-state activities, the team may also include individuals from outside California. Teams may include individuals from both non-profit and commercial institutions. To facilitate collaboration, CIRM will also provide funds for enhancing communication among team members through meetings and telecommunications.

The intent of this initiative is not to fund open-ended research, but to fund work that follows a careful, detailed and plausible strategy with defined milestones. The project will be expected to have a comprehensive plan, including specific goals with a road map and timeline for achieving them. Each phase of the work should be clearly described within the plan, with the activities of relevant personnel described, along with specific objectives and milestones for each phase of the work. A key aspect of the initiative will be the insistence by CIRM on strong management of the project. The team may wish to include an experienced project manager. Progress and overall strategy will be closely and regularly evaluated by a group that includes the manager, key scientific personnel, outside experts and CIRM staff.

Proposed CIRM Activities

1. RFA for interdisciplinary teams

Estimated Funding Allocations

1. CIRM intends to award four-year grants for interdisciplinary teams. Rounds of grants will be released in 2009 and 2012; annual funding will be up to \$7.5 million.

Total estimated cost - \$60 million

Tools / Technologies and Infrastructure

Initiative: Tools and Technologies

Significance and Objectives

Rapid progress in the research and development of stem cells will be facilitated by the development and availability of specialized tools and technologies. Scientists working in the field have highlighted a number of specific tools that are of such scope, require such specialized expertise and/or are so expensive that they are beyond the ability of many institutions to provide or develop on their own. Such tools include: microarrays for fingerprint analysis of stem cell and stem cell derivatives at different stages of development; vector based siRNA libraries for functional genomics studies; bioinformatics tools for the collection, sharing and analysis of large datasets; access to standardized reagents, particularly growth factors, for cell culture; and development of new markers for identification, selection, purification, trafficking and/or functional analysis. Markers include new tags for imaging and libraries of monoclonal antibodies against stage specific cell surface markers. Monoclonal antibodies will be important not only for the identification, selection and purification of stem cells and differentiated derivatives but also may, in some instances, have application as a therapeutic or diagnostic.

Similarly, the development and availability of new technologies will be important for advancement in stem cell science. For example, the field needs better imaging technologies that allow tracking of cell delivery, trafficking and activity, not only in small animal models but also in large animals and importantly, in patients. Improved imaging technologies for preclinical use could allow researchers to better predict how a therapeutic candidate will perform clinically, and more accurately assess its safety, efficacy, and potential for long-term effects. In addition, new cell separation technologies for production are needed that allow rapid separation of a given cell population with high purity and full retention of function. Similarly, at laboratory scale, cell separation technologies that enable separation of a rare population from small numbers of cells would be very useful. Nano-technology approaches are potentially powerful tools for stem cell biology because they can be used to control cell microenvironment interactions (e.g., between cells, between cells and the extracellular matrix, and between cells and soluble factors) and to miniaturize assays for high-throughput experimentation. Other technologies of importance in stem cell science include: delivery technologies, such as encapsulation; scaffolds and tissue engineering to mimic the natural tissue environment, thereby promoting function and survival; and micromanipulation technologies for cells including robotics.

CIRM intends to support tool and technology research and development that can serve the goals of the stem cell community and contribute to the advancement of stem cell science. In instances where tools already exist, CIRM may work with suppliers to access tools such as

reagents. CIRM also intends to fund the research and development of new technologies and tools identified as being important to the advancement of stem cell science. CIRM will periodically conduct multi-disciplinary workshops that bring together persons of disparate expertise (e.g., clinicians, basic scientists and engineers) from both academia and industry to brainstorm tool and technology solutions to stem cell biological / biomedical problems. CIRM believes that multi-disciplinary expert participation is crucial to successful tool and technology research programs. CIRM will encourage and may require multi-disciplinary collaboration in certain of the tools and technology research and development programs that it funds. Dynamic interaction with companies and relationships with commercial players may also be needed to facilitate technology development.

Proposed CIRM Activities

1. RFPs to source key available key tools including reagents.
2. Conduct multi-disciplinary workshops to define state of art and needs for key tools and technologies.
3. RFAs to conduct research and development of key tools and technologies with funding for 2 years. Multidisciplinary collaboration and collaboration between academia and industry will be encouraged.

Estimated Funding Allocations

1. CIRM intends to release a series of RFPs to identify available tools, for a grand total of \$2.8 million.
2. CIRM estimates the costs of the five proposed workshops at \$100,000 each.
3. CIRM intends to award multiple two-year grants. Awards will be made in 2008, 2010, 2012, 2014 and 2016, for annual funding of \$10 million and a total cost of \$80 million.

Total estimated cost - \$83.3 million

Initiative: Cores

Significance and Objectives

The conduct of science today is a complex endeavor where the availability of specialized tools, technologies and expert services can promote more rapid research and development in stem cell science by facilitating broader access through “cores”. Examples of cores, highlighted by interviewees, meeting speakers and participants as important for advancing stem cell science, include the following: high-throughput screening, vectors, specialized

small animal disease/injury model cores, stem cell bank(s) and flow cytometry. Another core mentioned often was a cell production core. Such cores could produce cells for research use and/or under Good Manufacturing Practices (GMP) for use in FDA-required preclinical safety studies and in human clinical studies. Production cores may include process development services such as developing master and working cell banks, developing scalable production processes and developing and performing qualification assays. A regulatory/clinical expert core service was also proposed that would address regulatory requirements, preclinical and clinical protocol design and data collection and analysis. Such a resource could also play a key role in working with regulatory authorities to help shape the regulatory requirements and guidelines in this new field of stem cell therapies.

CIRM intends to have an initiative that will periodically put out RFA(s) to address core resource needs identified as important to the rapid advancement of stem cell science. Depending on the nature of the core, it may be based in a single, few or multiple sites, with site, regional and/or state-wide use. Again, depending on the nature of the core, it may be made available through a non-profit research institution or in a for-profit institution or in both. CIRM will conduct workshops as needed to best assess core needs and options. In general, establishment of cores or identification of sources of core resources should be completed or in progress by 2011 to facilitate rapid development of stem cell R&D. An early priority is for a core stem cell bank, further discussed below.

Development of high-throughput technologies has enabled scientists to study cells simultaneously under a multitude of conditions and test their responses against entire libraries of compounds over a short period of time. These technologies, however, generate vast amounts of data that require time-consuming analysis. Scientists have a clear need for bioinformatics tools that will permit them to extract meaningful information from complex data sets in order to propose new hypotheses. As a result, CIRM treat the development of such tools as another early priority. Of particular interest are bioinformatics tools that could aid, for example, in deciphering lineage specification and differentiation programs of stem cells, identifying tumorigenic or pluripotent properties of cells, or identifying therapeutic targets.

CIRM intends to support core resources through grants and contracts. Such funding may be used to support operational expenses of cores critical to stem cell research, particularly where such cores can not be supported by federal funds. The funding is also anticipated to support, in some instances, expansion and/or establishment of core resources. CIRM support for access to core resources will exist as a component of other initiative RFAs such as the RFA discussed under the Clinical Research initiative, where GMP production of a given cell product is required.

Proposed CIRM Activities

1. Stem cell bank (see below)
2. Support the development of bioinformatics tools for management and analysis of genomic, proteomic, and other complex data to accelerate stem cell research and therapeutic development. Bioinformatics tools developed under this initiative must be freely available to scientists.
3. Conduct more in-depth research, including workshops and site visits to better define near term priorities and needs as well as existing assets and capabilities.
4. RFA(s) for priority core resources defined by (2) to be established and/or in progress by 2012.

Estimated Funding Allocations

1. Stem cell bank (see below)
2. CIRM plans to support two-year awards each year from 2007 to 2016 for the development of bioinformatics resources for a total of \$40 million
3. CIRM estimates the costs for the workshops and site visits it plans to assess needs and capabilities at roughly \$100,000 each in 2007 and 2009.
4. CIRM plans to award a number of grants for the development and operation of research cores. Funding could begin in 2007; total funding is anticipated to be up to \$87 million (not including facilities and major equipment costs)

Total estimated cost - \$107.2 million (not including \$35 million for facilities costs such as remodelling and large equipment purchases)

Initiative: Banks

Significance and Objectives

One of the issues facing stem cell researchers in California is the lack of a single, centralized source of non-federally approved stem cell lines for research. While the WiCell Research Institute has been contracted by the NIH to create a National Stem Cell Bank, which will involve the collection, characterization, and eventual distribution of as many federally-approved stem cell lines as possible, no similar, large-scale resource for non-federally-funded lines exists in the country. In addition to not being housed in a single location, currently available non-federally-funded lines reflect a spectrum of derivation techniques and growth conditions, which can make it difficult to make meaningful comparisons between and among specific cell lines.

California researchers also face the need for a consolidated, robust, easily accessible data bank for information regarding available cell lines, including characterization data, such as karyotype, antibody markers, and gene expression profiles, as well as other relevant details about their derivation, passage number, etc. As with the lack of standardization for the derivation and growth of stem cell lines, the lack of standardized data regarding those cell lines is also proving to be an impediment to researchers' efforts to study and draw meaningful conclusion about different stem cell lines.

The creation of a stem cell bank, which would house and distribute lines derived and characterized using standard protocols and be easily and readily accessible to researchers across the state, would be a valuable asset to California researchers. Similarly, the development of a data bank to house information about those lines (and others) would be beneficial as well.

Proposed CIRM Activities

1. Development of a stem cell bank to house and characterize (in a centralized, reliable and reproducible manner) a set of hESC lines and manage their maintenance and distribution for use by researchers in California and beyond.
2. Development of a freely available, web-accessible database/knowledgebase of available human embryonic stem cell lines that includes characterization data such as gene expression profiles, specific complement of cell-surface markers, and differentiation capabilities under specific cell culture conditions.

Estimated Funding Allocations

1. CIRM has allocated \$20 million from 2007 to 2016 for the creation and operation of a stem cell bank.
2. CIRM has allocated additional funding in years 2009 to 2016, for the development and maintenance of a knowledge base associated with the cell bank, for a total of \$3.4 million.

Total estimated cost - \$23.4 million

Facilities

Initiative: Laboratories / Research Facilities

Significance and Objectives

The long-term funding provided by Proposition 71 will fuel a dramatic expansion in stem cell research in California. The number of investigators doing stem cell research in California will increase significantly through recruitment of new investigators from out of state and through training of new investigators supported by CIRM's Training Program. Since the research that they will conduct will represent a net addition to the total biomedical research effort within the state, new facilities will be required to house these investigators. Moreover, it will be advantageous to develop dedicated space for stem cell research to facilitate scientific interaction and sharing of common equipment. Finally, present federal policy prohibits the use of any space whose construction or renovation was funded by the NIH or which is supported by NIH indirect costs for research outside the federal guidelines for human embryonic stem cell research. For these reasons, it will be important to the achievement of the goals of CIRM to support the construction and renovation of space for research. In addition, CIRM may wish to provide large equipment grants for the specialized needs of stem cell research.

CIRM recognizes that different institutions have different capabilities and needs for research space. Large institutions or consortia of institutions may serve literally scores of stem cell researchers, while other institutions may have programs of equally high quality, but of smaller scale. CIRM thus plans to offer grants at several levels to accommodate these needs. The Institute envisages offering large grants (tens of millions of dollars) to five or more large institutions for new buildings in which all or a substantial part (e.g., one wing) would be dedicated to stem cell research. Smaller grants (five to ten million dollars) will also be offered to a number of institutions who may wish to renovate a more modest area (ca. 10,000 square feet) for stem cell research. Finally, through the RFA to be issued shortly, CIRM will support grants of roughly \$2 million to renovate space for shared research laboratories suitable for culturing human embryonic stem cells.

Proposed CIRM Activities

1. RFA under the Innovation Initiative for Shared Research Laboratory Space (already completed).
2. RFA for major facilities, tiered to accommodate both large and small institutions.

Estimated Funding Allocations

1. CIRM intends to provide a total of \$16.3 million in facilities as part of its shared research laboratory grants program.
2. CIRM plans to award several large facilities grants, with funds to be distributed between 2007 and 2009, for a grand total of \$150 million.
3. CIRM plans to award several smaller facilities grants, with funds to be distributed between 2007 and 2009, for a grand total of \$50 million.
4. CIRM intends to provide a total of \$35 million in facilities support as part of its cores program.
5. CIRM plans to maintain a facilities contingency fund for unforeseen facilities needs.

Total estimated cost - \$251.3 million (excluding contingency fund)

Communities of Science

Initiative: Journal / Web Portal

Significance and Justification

Communication of research findings is an essential means of accelerating our progress towards stem cell-derived therapies and diagnostics. New data and knowledge produced through sponsored research must be available to the scientific community to encourage further refinement of established ideas and stimulate development of new concepts. Immediate access to published, peer-reviewed materials is one mechanism for enhancing scientific communication, not only among researchers but also with the public. The fruits of research that is funded with public monies should be accessible to the public that made the work possible. Toward these ends, CIRM intends to support a collaborative effort to establish a peer-reviewed journal for stem cell research, similar to those published by the Public Library of Science (PLOS) or BioMed Central, that will provide scientists with an immediate-access option that is of high quality. In order to reach wide readership, the journal must be web-accessible, freely-available, and may also include a print version.

An important feature of many of these journals is interpretative material that explains in lay terms the scientific significance of a particular paper and the implications of the research. Articles of this sort that are oriented toward patients are particularly useful for clinical studies. CIRM would offer support for these journals by directly supporting the production of this material and by paying authors' fees for CIRM scientists who submit work to them.

Because web-based, open access journals make material immediately available without charge, CIRM would be both accelerating scientific progress and fulfilling its mandate to inform the public by supporting such a journal.

Open access to published, peer-reviewed materials is one obvious mechanism for enhancing scientific communication. Relevant research data and knowledge from around the world will nevertheless continue to be placed in journals that range from the most obscure to the most widely read. In some cases, key information may not be published at all, particularly if such data are not directly tied to an original body of work. Thus, an important additional mechanism to aid communication is the creation of a central resource of organized and managed data for scientists.

Interest in a web-accessible database or knowledgebase of available human stem cell lines, for example, has already been expressed by many stem cell researchers. Such a database, to be useful, must be supported by a centralized effort to characterize stem cell lines in a reliable and reproducible manner that permits at least a qualitative comparison of all studied lines. Knowledge of gene expression profiles, specific complement of cell-surface markers, and differentiation capability under specific culture conditions, for example, is helpful to scientists developing research studies with specific stem cell lines.

Similarly, a database/knowledgebase of available research tools such as antibodies, cell-surface markers, and culture media components may prove useful. Such communications tools should not only serve California scientists but also bring knowledge from around the world to accelerate our progress towards therapies and cures.

Proposed CIRM Activities

1. Develop, with suitable partners, a web-based, open-access scientific journal.
2. Database / knowledgebase of available stem cell lines (see "Banks" initiative)
3. Support the development of a freely available, web-accessible database/knowledgebase of stem cell research tools (e.g., antibodies, siRNA, culture components) to increase knowledge of and access to valuable reagents and methods.

Estimated Funding Allocations

1. CIRM has allocated funds from 2007 to 2016 for the development and maintenance of an online journal, for a total of \$2.75 million.
2. Database / knowledgebase of available stem cell lines (see "Banks" initiative)

3. CIRM has allocated funds from 2007 to 2016 for the development and maintenance of a web portal to provide access to stem cell research tools, for a total of \$2.85 million.

Total estimated cost - \$5.6 million

Responsibility to the Public

Initiative: Public Outreach

Significance and Justification

To an unusual degree, stem cell research is in the public eye. Its progress is keenly followed not only by scientists and clinicians, but by ethicists, legislators, politicians, social scientists, and those interested in public policy. Most importantly, patients and their families feel a deep involvement in stem cell research. The engagement, support and interest of this broad constituency are a great strength for CIRM. It also confers a responsibility for the Institute to communicate and interpret the results of stem cell research in many venues and to be aware of its broad impact on society; effective communication that fosters awareness is an imperative for CIRM.

CIRM's responsibility to the public includes promoting the public's awareness and understanding of the fundamental science and issues surrounding stem cell research. In addition, CIRM needs to keep the public informed of the many challenges faced by scientists and clinicians in therapy development and the impact and potential of research findings. One of the best ways to achieve these goals is to recruit the stem cell scientific community in efforts to share information with the public directly. To do so effectively, scientists must develop the necessary communication skills that permit and enhance their ability to deliver new findings and complex concepts in lay terms. As part of its training and career development programs, CIRM will support forums in which scientists can present their work in a format that is easily accessible to the public.

CIRM will also provide support to develop educational materials (e.g., videos, textbooks) and public outreach programs that provide expert seminars, presentations, and/or immersion opportunities to diverse communities throughout California.

Proposed CIRM Activities

1. Support work to develop educational materials on stem cell research such as textbooks, videos, and web tools.
2. Support open access web-based and/or print reviews of stem cell research aimed for consumption by the lay public.

Estimated Funding Allocations

1. CIRM plans to award grants for the development of stem cell-related educational materials, for a total of \$1.5 million.
2. CIRM will allocate funding from 2007 to 2016 to support the creation and maintenance of web-based information resource for the general public, for a total of \$2.5 million

Total estimated cost - \$4.5 million

Initiative: Stem Cell Research and Society: Implications and Impact

Significance and Objectives

Stem cell research not only offers the possibility of medical benefit, but will also influence society in other ways. Stem cell research raises important ethical questions. Some are related to egg donation. What are the medical and psychological consequences of donating eggs for research? Are current informed consent procedures adequate? Do donors understand what they are agreeing to? Other questions relate to how stem cells are used. Is privacy protected? When does xenotransplantation raise ethical questions? When stem cell therapies become available, other types of questions will arise. If therapeutic material is limited, who will decide and how will it be decided which patients receive treatment? How can the entire population be served regardless of genotype? How will stem cell therapies be paid for? Many of these issues raise questions of law and public policy. To address these matters, CIRM will sponsor both empirical research and also may sponsor studies or conferences that will take a more theoretical approach.

Proposed CIRM Activities

1. Ethical studies related to egg donation, which may be incorporated into biological investigations that involve egg donation or may be funded separately.

2. Studies and conferences on social, legal, economic consequences and on other ethical problems.

Estimated Funding Allocations

1. CIRM plans to award three-year grants for ethical studies related to egg donation for a total of \$7.5 million.
2. CIRM plans to award up to \$3 million / year for six years to support the study of social, legal, economic consequences of stem cell research, for a total of \$18 million.

Total estimated cost - \$25.5 million

Initiative: Economic Impact

Significance and Objectives

Proposition 71 has an explicit commitment for an economic return to the State from stem cell research and states as an explicit aim the desire to advance the California biotechnology industry. Studies by independent, outside experts aimed at assessing the economic impact of stem cell research in California will be very important as the project matures.

Proposed CIRM Activities

1. RFA for preliminary studies to set the metrics by which the economic impact of CIRM's activities will be measured.
2. RFA for the completion of an economic impact study.

Estimated Funding Allocations

1. CIRM plans to make one award in the amount of \$300,000 in 2007 to define the metrics for future economic impact studies.
2. CIRM plans to make two, \$1 million awards, one in 2011 and one in 2016, for the conduct of an economic impact study.

Total estimated cost - \$2.3 million

Short-term, Mid-term, Long-term Priorities

All the initiatives that CIRM will support are important. Though their priority levels may vary, at any one time, the majority of CIRM's initiatives will be classified as high priority. As has been shown above, however, the priority assigned to an initiative may change over time, giving it a unique "priority profile". An initiative's priority profile is based on two factors. The first is its direct impact on CIRM mission's to support the discovery and development of cures and therapies; in this regard, most of CIRM's initiatives are classified as high priority. The second consideration is a practical one: timing. Different initiatives will be more or less important at different phases of our work. For example, the Facilities initiative will be critically important early on, but less so in later years. Other initiatives will increase in priority with time: the Preclinical Product Development and Clinical Investigation initiatives will become higher priorities as CIRM approaches the mid-term, when more and more therapies will have reached the phase of pre-clinical development simply because time will be required for the field to advance to a point where substantial support for such initiatives is necessary and possible.

The following table details CIRM's priorities in the short-, medium- and long-term (please note that the same initiative may appear multiple times in different parts of the table):

	Short-Term Year 1 - Year 3	Medium-Term Year 4 - Year 6	Long-Term Year 7 - Year 10
Highest Priority Initiatives	<p>Banks Biology of Stem Cells Disease Teams Generation and Use of Disease Specific Cell Lines hESC Jump Start Initiative Interdisciplinary Research Teams Journal / Web Portal Laboratories / Research Facilities New Methods for Development of Stem Cell Lines Public Outreach Scientific Personnel Development Scientist Training / Internships Technical Staff Training Tools and Technologies Translational Research</p>	<p>Banks Bio-process Engineering and Automation Clinical Investigation Cores Disease Teams Generation and Use of Disease Specific Cell Lines hESC Jump Start Initiative Immune Tolerance Interdisciplinary Research Teams Journal / Web Portal Preclinical Product Development Public Outreach Scientific Personnel Development Scientist Training / Internships Stem Cell Based Tissue Engineering in Regenerative Medicine Translational Research</p>	<p>Banks Clinical Investigation Disease Teams hESC Jump Start Initiative Immune Tolerance Interdisciplinary Research Teams Journal / Web Portal Preclinical Product Development Public Outreach Translational Research</p>
Other Initiatives	<p>Bio-process Engineering and Automation Clinical Investigation Cores Egg and Embryo Research Immune Tolerance Preclinical Product Development Stem Cell Based Tissue Engineering in Regenerative Medicine</p>	<p>Biology of Stem Cells Egg and Embryo Research Laboratories / Research Facilities New Methods for Development of Stem Cell Lines Technical Staff Training Tools and Technologies</p>	<p>Biology of Stem Cells Bio-process Engineering and Automation Cores Egg and Embryo Research Generation and Use of Disease Specific Cell Lines Laboratories / Research Facilities New Methods for Development of Stem Cell Lines Scientific Personnel Development Scientist Training / Internships Stem Cell Based Tissue Engineering for Regenerative Medicine Technical Staff Training Tools and Technologies</p>

Table 2: Overview of prioritization of CIRM initiatives

In the same way that CIRM's initiatives will evolve over time to adapt to changing scientific opportunities and challenges, the relative priority of different initiatives may also change.

Short-term, Mid-term, Long-term Budget Projections

The development of Scientific Strategic Plan was accompanied by the development of a 10-year budget. CIRM's budget projections, while preliminary and subject to change, are intended to reflect the amount of funding that will be allocated to each category of initiatives over the next ten years. The amounts assigned to each category vary, which reflects the diverse nature of the research activities to be supported by CIRM. This variability is the result of many factors, including the number, size, and duration of the grants to be awarded as well as the nature of the work to be performed under the purview of each category.

The development of the plan's budget projections was also guided by the financial controls in Proposition 71, including the following (See Appendix D-1 for a more detailed review of these financial controls):

- The maximum amount of new bonds that can be issued is capped at \$350 million per calendar year; if less than this amount of bonds is issued in any year, the remaining authorized amount may be carried forward.
- No more than 3% of the proceeds of the bonds authorized shall be used for the costs of general administration of the Institute.
- No less than 97% of bond proceeds after issuance and interest costs will be used for research and facilities grants and grant oversight.
- No more than 3% of this 97% may be used for research and research facilities implementation costs.
- Up to 10% of this 97% may be used for research facilities grants.
- No less than 90% of this 97% will be used for research grants.
- Annual (calendar year) commitments are subject to a stipulated maximum (see chart); however, uncommitted funds may be carried forward to subsequent years.

"Duplication should be avoided. One dollar duplicated is one dollar wasted. If we can fund something that is too early for industry that's where we should be. If industry can not justify the financial risk of early experiential clinical trials, we should fund those studies. We should always look for the gaps in funding where we can have an impact on advancing the field"

***- Duane Roth,
ICOC Member***

Annual Maximum Commitments (not inclusive of carry over)						
2005	Year 1	5.6%		2010	Year 6	11.3%
2006	Year 2	9.4%		2011	Year 7	11.3%
2007	Year 3	9.4%		2012	Year 8	11.3%
2008	Year 4	11.3%		2013	Year 9	11.3%
2009	Year 5	11.3%		2014	Year 10	7.5%

The following table (Table 3) details the allocation of CIRM funding over time across the three segments of our framework that define the pathway from basic science to the clinic (See Appendix D-2 for more detailed budget projections).

The amount committed to early-stage research reflects the state of development of the field and the need to build fundamental knowledge, as described in the "Laying the Foundation" section of the plan; funds for the pre-clinical stage reflect the high cost of pre-clinical research and the growing number of therapies that will be developed as time progresses. Although clinical research is most expensive, the long time course of therapy development means that most of these costs will occur after the ten-year time frame of this plan. The funding allocated to clinical research reflects this, as well as the fact that CIRM will support primarily Phase I trials, where costs are lower, and that CIRM expects to share the costs of later stage clinical trials with industry.

Initiative	Laying the Foundation	Preparing for the Clinic	Clinical Research	Total
Research Activities				
Scientific Training and Development	Total for Resource Category			\$ 295.0
Scientist Training / Internships	\$ 94.2	\$ 31.4	\$ 31.4	\$ 157.0
Technical Staff Training	\$ 38.0	\$ -	\$ -	\$ 38.0
Scientific Personnel Development	\$ 33.3	\$ 33.3	\$ 33.3	\$ 100.0
Innovation Science	Total for Resource Category			\$ 376.8
hESC Jump Start Initiative	\$ 81.2	\$ 27.1	\$ 27.1	\$ 135.3
Annual Innovation Grants	\$ 89.1	\$ 29.7	\$ 29.7	\$ 148.5
Biology of Stem Cells	\$ 75.3	\$ -	\$ -	\$ 75.3
Egg and Embryo Research	\$ 17.7	\$ -	\$ -	\$ 17.7
Mission-Directed Science	Total for Resource Category			\$ 1,272.1
New Methods for Development of Stem Cell Lines	\$ 8.2	\$ 4.1	\$ -	\$ 12.3
Stem Cell Based Tissue Engineering in Regenerative Medicine	\$ 43.7	\$ 43.7	\$ -	\$ 87.4
Translational Research	\$ 138.8	\$ 323.8	\$ -	\$ 462.6
Generation and Use of Disease Specific Cell Lines	\$ 15.2	\$ 15.2	\$ -	\$ 30.4
Immune Tolerance	\$ 20.1	\$ 30.2	\$ 10.1	\$ 60.4
Bio-process Engineering and Automation	\$ -	\$ 60.0	\$ -	\$ 60.0
Preclinical Product Development	\$ -	\$ 108.0	\$ -	\$ 108.0
Clinical Investigation	\$ -	\$ -	\$ 451.0	\$ 451.0
CIRM Special Programs	Total for Resource Category			\$ 182.0
Disease Teams	\$ 24.4	\$ 48.8	\$ 48.8	\$ 122.0
Interdisciplinary Research Teams	\$ 24.0	\$ 24.0	\$ 12.0	\$ 60.0
Tools / Technologies and Infrastructure	Total for Resource Category			\$ 213.9
Tools and Technologies	\$ 41.7	\$ 41.7	\$ -	\$ 83.3
Cores	\$ 53.6	\$ 53.6	\$ -	\$ 107.2
Banks	\$ 11.7	\$ 11.7	\$ -	\$ 23.4
Communities of Science	Total for Resource Category			\$ 5.6
Journal / Web Portal	\$ 1.9	\$ 1.9	\$ 1.9	\$ 5.6
Responsibility to the Public	Total for Resource Category			\$ 32.3
Public Outreach	\$ 1.5	\$ 1.5	\$ 1.5	\$ 4.5
Stem Cell Research and Society: Implications and Impact	\$ 8.5	\$ 8.5	\$ 8.5	\$ 25.5
Economic Impact	\$ 0.8	\$ 0.8	\$ 0.8	\$ 2.3
Totals	\$ 822.8	\$ 898.9	\$ 656.0	\$ 2,377.7
Facilities				
Facilities				
Laboratories / Research Facilities	\$ 190.9	\$ 81.8	\$ -	\$ 272.7
Totals	\$ 190.9	\$ 81.8	\$ -	\$ 272.7

Table 3: Overview of general funding allocations for CIRM initiatives

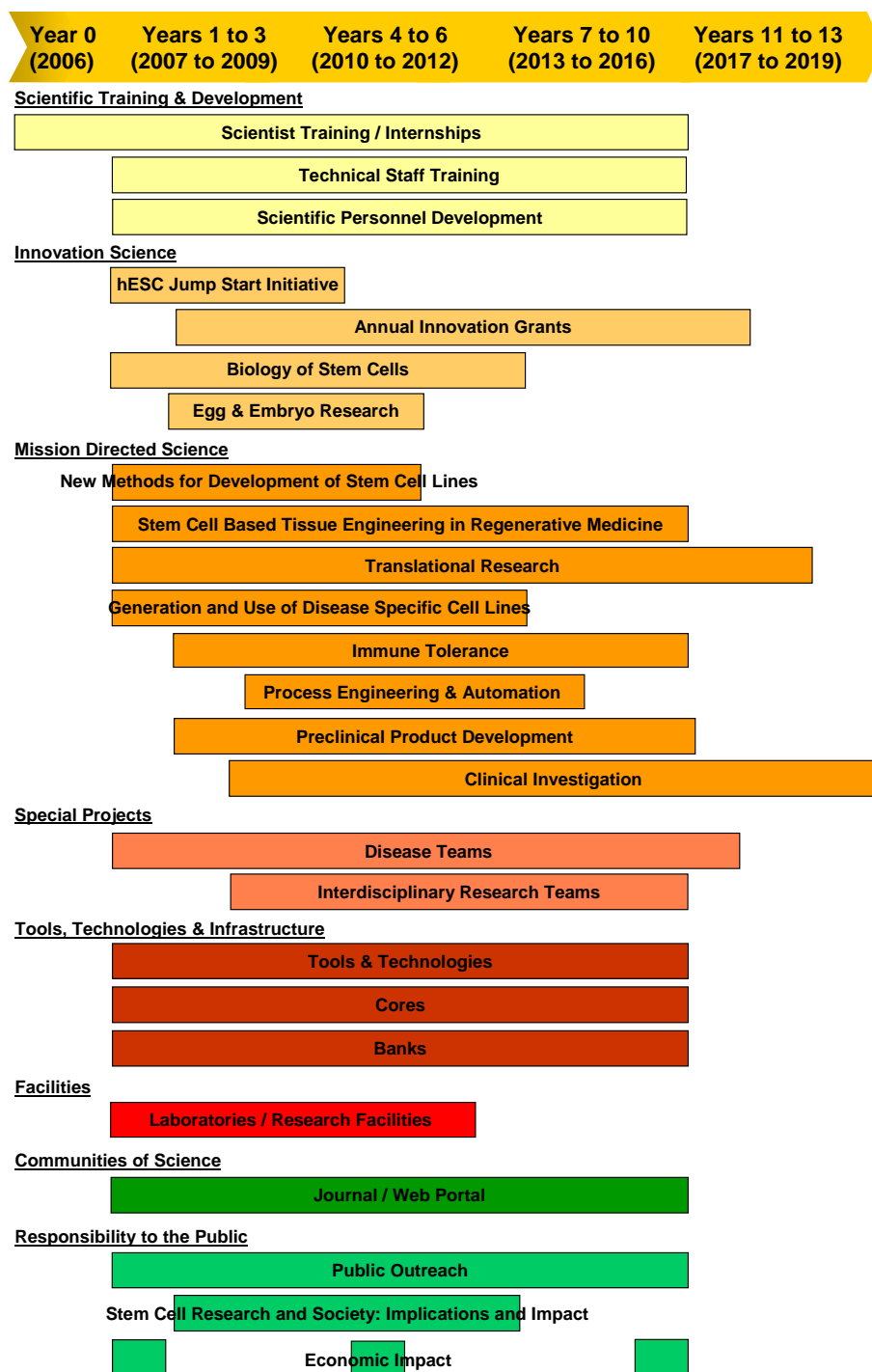


Figure 6: Timing of proposed initiatives

A Fast Start: The First 1000 Days

To be written after the October 10 and 11, 2006 ICOC meetings.

A Living Plan: Assessment and Revision

Aim

The California Institute for Regenerative Medicine's strategic plan will be a living plan - flexible in response to its successes and failures, and opportunistic in capitalizing on unforeseen scientific developments. Through periodic assessment and review, CIRM will measure the progress of the Institute against the five and ten year goals set forth in the scientific strategic plan and, in the broader context of the entire field of stem cell research, periodically reassess the focus of the plan and the strategic objectives that it seeks to attain.

"CIRM needs to periodically assess itself and look at itself and make sure it's still involving the stakeholders and being true to its mission."

***- Jonathan Shestack,
ICOC Member***

A detailed operational plan for the first three years is given in the preceding section, entitled "The First 1000 Days". As CIRM moves forward, it will need to project similar plans for future years. We propose that the ICOC conduct a review of progress at three years and at seven years of the ten year time span covered by the strategic plan, with the purpose of assessing progress, modifying the five and ten year commitment goals as necessary. On the basis of the revised plan, the CIRM staff can prepare for ICOC approval a new three year operational plan

Goals of the Evaluation and Review⁴

Assessment will focus on ensuring that progress towards the five and ten year commitment goals of CIRM is being made and that the program is consistent with CIRM's mission and core values/principles, particularly those of remaining "Accountable", "Adaptable" and "Innovative." Additional goals of the assessment will be as follows.

- To provide performance data at years 3 and 7 of the Institute's strategic plan that will enable the Institute to make changes, address "critical gaps" and remain flexible and responsive to a rapidly changing research landscape.
- To demonstrate careful and effective stewardship of California taxpayer dollars and ensure that the regulatory framework established through its ethics and administrative policies are upheld.
- To provide mechanisms to identify program accomplishments to partner organizations nationally and internationally, as well as in California.

⁴ Fogarty International Center *Framework for Program Assessment (Evaluation and Review)*-National Institutes of Health

Mechanism for Revision

- A review will be conducted at years 3 and 7 of the plan by an blue-ribbon, outside committee composed of scientists, clinicians, ethicists and patient advocates both from within and from outside of California. The review will track CIRM's progress against its stated commitments and, more broadly, its values and strategic principles and will make recommendations for modifications of the plan.
- Assessment will rely on progress reporting from CIRM grantees and may include, at CIRM's discretion, other methods of evaluation including, but not limited to, surveys, interviews, focus group discussions, advisory committee reviews, conferences.
- CIRM may also wish to sponsor a scientific conference similar to the scientific conference held in 2004 "Stem Cell Research: Charting New Directions for California" to gather information on the state of the field both in California as well in the rest of the country on which to base an assessment of:
 - Whether funding priorities identified in this strategic plan reflect the state of the field in general and;
 - Remain responsive to CIRM's mission of effectively advancing the science of stem cell research in California to affect cures.
- The review will be reported to the ICOC who will consider the recommendations made in the review and, on that basis, approve modifications to the strategic plan.
- CIRM staff, under the leadership of the President, will propose a 3-4 year operational plan based on the strategic plan as modified by the ICOC.

Appendices

Appendix A-1: Strategic Planning Advisory Committee (SPAC) Roster

SPAC Member Roster	
Member	Title(s) and Affiliation(s)
David Baltimore, PhD	Member, Independent Citizens' Oversight Committee of CIRM President, California Institute for Technology
Paul Berg, PhD	Alternate Member, Independent Citizens' Oversight Committee of CIRM Cahill Professor of Biochemistry, Emeritus, Stanford University School of Medicine
George Daley, MD, PhD	Associate Professor of Pediatrics and Biological Chemistry, Boston Children's Hospital and Harvard Medical School Associate Director, Stem Cell Program at Children's Hospital Boston
Steve Forman, MD	Professor, Hematology / Hematopoietic Cell Transplantation, City of Hope National Medical Center Chair, Division of Hematopoietic Cell Transplantation, City of Hope National Medical Center
Zach W. Hall, PhD (Chair)	President, California Institute for Regenerative Medicine
Robert N. Klein	Chairman, Independent Citizens' Oversight Committee of CIRM
Sherry Lansing	Member, Independent Citizens' Oversight Committee of CIRM Founder / CEO, The Sherry Lansing Foundation
Ed Penhoet, PhD	Vice-Chairman, Independent Citizens' Oversight Committee of CIRM President, Gordon and Betty Moore Foundation
William Rastetter, PhD	Former President and CEO Biogen Idec
Jeff Sheehy	Member, Independent Citizens' Oversight Committee of CIRM Communications Director UCSF AIDS Research Institute

Appendix A-2: Strategic Planning Advisory Committee (SPAC) Meeting Dates and Topics Discussed

SPAC Meeting Dates and Topics Discussed	
Date	Topic(s) Discussed
May 1, 2006	<ul style="list-style-type: none">▪ Kick Off Meeting
May 29, 2006	<ul style="list-style-type: none">▪ Funding Mechanisms for the Private Sector▪ New ESC Cell Lines: Focus for Early Funding?
June 13, 2006	<ul style="list-style-type: none">▪ Cord Blood: CIRM's Role?▪ Databank for hESC lines?
July 10, 2006	<ul style="list-style-type: none">▪ Technologies for Stem Cell Research▪ Training
August 21, 2006	<ul style="list-style-type: none">▪ Clinical Trial Development: CIRM's Role?
August 24, 2006	<ul style="list-style-type: none">▪ Review of Scientific Strategic Plan Outline
September 15, 2006	<ul style="list-style-type: none">▪ Review of Drafts of Selected Sections of Plan

Appendix A-3: Summary of External Inputs Including Interviews

- Potential interviewee pool: ~ 200
- Interviews completed to date: 70 separate interviews completed with a total of 73 individuals

Interviewee	Affiliation
Bruce Alberts, Ph.D.	President, National Academy of Sciences; Chair, National Research Council
David J. Anderson, Ph.D.	Investigator, Howard Hughes Medical Institute; Professor, California Institute of Technology
Peter Andrews, Ph.D.	Professor, University of Sheffield (UK)
David Baltimore, Ph.D.	President, California Institute of Technology
Nissim Benvenisty, M.D., Ph.D.	Professor, The Hebrew University of Jerusalem
Paul Berg, Ph.D.	Cahill Professor of Biochemistry, Emeritus, Stanford University School of Medicine
Melissa Carpenter, Ph.D.	Vice President, CyThera, Inc.
Susan Desmond-Hellmann, M.D., M.P.H.	President of Product Development, Genentech Inc.
Kevin Eggan, Ph.D.	Assistant Professor, Harvard University; Assistant Investigator, Stowers Medical Institute
Marcy Feit, RN, M.S.N.	Patient Advocate, ICOC; President and Chief Executive Officer, Valley Health Care Systems
Susan Fisher, Ph.D.	Professor, University of California, San Francisco
Garret A. Fitzgerald, M.D.	Director, Institute for Translational Medicine and Therapeutics, University of Pennsylvania
Susan Berke Fogel, J.D.	Co-founder, Pro-Choice Alliance for Responsible Research
James R. Gavin III, M.D., Ph.D.	Interim President and Chief Executive Officer, Microlslet, Inc.; Clinical Professor, Emory University; Executive Vice President, Healing our Village, LLC
Lawrence S.B. Goldstein, Ph.D.	Professor, UCSD; Investigator, Howard Hughes Medical Institute
Hank Greely, J.D.	Professor, Stanford Law School
Robert G. Grossman, M.D.	Director, The Neurological Institute; Chairman, Department of Neurosurgery, The Methodist Hospital

Interviewee	Affiliation
Jack Harding, Ph.D.	Health Scientist Administrator, National Center for Research Resources at the National Institutes of Health
Edward Holmes, M.D.	Vice Chancellor and Dean, University of California at San Diego Health Sciences
Katie Hood, M.B.A.	Acting Chief Executive Officer, Michael J. Fox Foundation for Parkinson's Research
Leroy Hood, M.D., Ph.D.	Founder and Director, Institute for Systems Biology
Mark B. Horton, M.D., M.P.H.	Public Health Officer, State of California
Richard Hynes, Ph.D.	Professor, The Massachusetts Institute of Technology; Investigator, Howard Hughes Medical Institute
Hugh Ilyine	Vice President and Chief Operating Officer, Stem Cell Sciences
Rosario Isasi, J.D., M.P.H.	Postdoctoral Fellow, University of Montreal
Robert N. Klein, J.D.	Chairman and Patient Advocate, ICOC; President, Klein Financial Corporation
Ihor Lemischka, Ph.D.	Associate Professor, Princeton University
Jeanne F. Loring, Ph.D.	Adjunct Associate Professor, Burnham Institute for Medical Research
Bert Lubin, M.D.	President, Children's Hospital Oakland Research Center
Daniel R. Marshak, Ph.D.	Vice President and Chief Scientific Officer, PerkinElmer Inc.; Former Senior Vice President and Chief Scientific Officer, Osiris Therapeutics Inc.
Jeffrey Martin, J.D.	Patient Advocate; Chairman of the Board, Parkinson's Action Network; Counsel, Goodwin Procter
Martin McGlynn	President and Chief Executive Officer, Stem Cells, Inc.
Colin McGuckin, Ph.D.	Professor of Regenerative Medicine, Newcastle University
Douglas A. Melton, Ph.D.	Thomas Dudley Cabot Professor of the Natural Sciences, Harvard University; Investigator, Howard Hughes Medical Institute; co-director of Harvard's Center for Genomic Research and the Harvard Stem Cell Initiative
Stephen L. Minger, Ph.D.	Director of Stem Cell Biology Laboratory, King's College, London
Jonathan Moreno, Ph.D.	Professor, University of Virginia; Director, Center for American Progress, Washington, DC
Sean Morrison, Ph.D.	Assistant Professor, University of Michigan Medical School
Peter Mountford, Ph.D.	Chief Executive Officer, Stem Cell Sciences
William Neaves, Ph.D.	President and Chief Executive Officer, Stowers Institute for Medical Research

Interviewee	Affiliation
Thomas Okarma, M.D., Ph.D.	President and Chief Executive Officer, Geron Corporation
Warren Olanow, M.D.	Professor and Chair, Mount Sinai School of Medicine
Gilbert S. Omenn, M.D., Ph.D.	Professor, University of Michigan; Former Executive Vice President and Chief Executive Officer, University of Michigan Health System
Per Peterson, M.D., Ph.D.	Chairman, Research & Development - Pharmaceutical Group, Johnson & Johnson
Francisco Prieto, Ph.D.	Patient Advocate, ICOC; President, Sacramento Sierra Chapter of the American Diabetes Association
Harriet Rabb, J.D.	Vice President and General Counsel, Rockefeller University
Martin Raff, M.D.	Professor, University College London
Mahendra Rao, M.D., Ph.D.	Vice President, Invitrogen Corporation; Formerly at NIA
Don Reed	Co-Founder, Californians for Cures; Patient Advocate - spinal cord injury
Jesse Reynolds, M.S.	Project Director, Biotechnology Accountability - Center for Genetics and Society
Janet Rossant, Ph.D.	Chief of Research, The Hospital for Sick Children; Deputy Director, Canadian Stem Cell Network
Duane Roth	Chairman and Chief Executive Officer, Alliance Pharmaceutical Inc.; Chief Executive Officer, CONNECT
Pablo Rubinstein, M.D.	Founder and Director, New York Blood Center - National Cord Blood Program
George Scangos, Ph.D.	President and Chief Executive Officer, Exelixis, Inc.
Edward Scolnick, M.D.	Director, Broad Institute; Former President, Merck Research Laboratories
Ira Shoulson, M.D.	Professor, University of Rochester Medical Center
John Simpson	Stem Cell Project Director, Foundation for Taxpayer and Consumer Rights
Glyn Stacey, Ph.D.	Head of Division of Cell Biology and Imaging, National Institute of Biological Standards and Control (UK)
Bruce Stillman, Ph.D.	President, Cold Spring Harbor Laboratory
Rainer F. Storb, M.D.	Head of Transplantation Biology Program, Fred Hutchinson Cancer Research Center
Lorenz Studer, M.D.	Assistant Member, Memorial Sloan-Kettering Cancer Center
Clive Svendsen, Ph.D.	Professor, University of Wisconsin

Interviewee	Affiliation
Joe Tayag	Health Program Coordinator, The Greenlining Institute
Marc Tessier-Lavigne, Ph.D.	Senior Vice President, Genentech, Inc.
Jeffrey M. Thompson, Ph.D.	Associate Provost for Research, California State University, San Bernardino
James A. Thomson, V.M.D., Ph.D.	Professor, University of Wisconsin; Scientific Director, WiCell Research Institute
Alan Trounson, MSc, Ph.D.	Scientific Director, Monash University, Australia; Founder and Executive Vice Chairman, The Australian Stem Cell Centre
Ann Tsukamoto, Ph.D.	Vice President, Stem Cells, Inc.
Harold Varmus, M.D.	President and Chief Executive Officer, Memorial Sloan-Kettering Cancer Center; Former Director, National Institutes of Health
Lydia Villa-Komaroff, Ph.D.	Chief Scientific Officer; Cytonome, Inc.
John Wagner, M.D.	Director and Professor, University of Minnesota
Gordon Weir, M.D.	Professor, Harvard University; Investigator, Joslin Diabetes Center; Section Head, Islet Transplantation and Cell Biology; Diabetes Research and Wellness Foundation Chair
Tadataka Yamada, M.D.	President of the Global Health Program, Bill and Melinda Gates Foundation; Former Chairman R&D, GlaxoSmithKline
Leonard Zon, M.D.	Investigator, Howard Hughes Medical Institute at Children's Hospital; Professor, Harvard University

Information Source	Relevant Date(s)	Total
Expert Interviews		
70 of the over 200 individuals identified with significant expertise in the science, policy, ethics, and industry involving SCR have been interviewed using a standardized format	March, 2006-August, 2006	70
Scientific Conferences		
"Charting New Directions"	Oct. 1-2, 2005	27
"Funding Mechanisms"	May. 25, 2006	5
"From Basic Research to the Clinic"	July. 13, 2006	5
"Industry Roundtable"	July. 25, 2006	8
Focus Groups		
Patient Advocate	July. 17, 2006	16
Diversity	August. 26, 2006	16
ICOC Strategic Planning Meetings		
Scientific and Medical Research Funding Working Group Meeting	June. 12, 2006	10
Strategic Plan Advisory Committee Meetings		
This 10-member committee met 7 times between May and September, 2006 to advise the strategic planning committee on key issues	May, 2006-September, 2006	10
Other		
Bay Area Workforce Funding Collaborative	August. 10, 2006	10
Myelin Repair Foundation	July. 18, 2006	3
CSU Group	August 28, 2006	10
		*190

*Note: This number is the total number of individuals who formally participated in these strategic planning events. This total reflects a degree of duplication given that some individuals were consulted in multiple contexts. This number is not inclusive of feedback we received from the public at these events. The source profile table below reflects actual numbers of those consulted to date.

Profile of individuals consulted to date	Total
Scientists/Clinicians	62
Prominent Scientific and Administrative Leader	5
Patient Advocates	17
Private Sector representatives	19
Foundation representatives	7
Public interest/Government representatives	45
ICOC members	13
Other	3
	171

Appendix A-4: Details on the Scientific Conferences

May 25, 2006: Funding Structures to Advance Stem Cell Research and Therapy		
Speaker	Affiliation	Title / Subject of Presentation
Michael Rudnicki, M.D., Ph.D.	University of Ottawa, Canada	"The Canadian Stem Cell Network"
Michael Amos, Ph.D.	Advanced Technology Program, National Institute of Standards and Technology	"The Advanced Technology Program: Innovative Technology Solutions Through Industry-led Public Private Partnerships"
Richard Insel, M.D.	Juvenile Diabetes Research Foundation	"Research Strategy and Funding Programs of the Juvenile Diabetes Research Foundation"
Ethan Signer, Ph.D.	High Q Foundation	"Managing the Search for Huntington Disease Therapy"
Jonathan Shestack	Cure Autism Now Foundation	N/A

July 13, 2006: The Scientific Challenge: From Basic Research to the Clinic		
Speaker	Affiliation	Title / Subject of Presentation
Stuart Orkin, M.D.	Harvard Medical School	"Stem Cells: Looking Back and Ahead"
Jill Heemskerk, Ph.D.	National Institute of Neurological Disorders and Stroke	"The SMA Project: A New Approach to Therapy Development at NIH"
Allen M. Spiegel, M.D.	Albert Einstein College of Medicine	"Delivering on the Promise of Stem Cell Research: What Will it Take?"
Stephen A. Sherwin, M.D.	Cell Genesys, Inc.	"The Development of Novel Cellular Therapeutics: Some Lessons from the Private Sector"
Joan Samuelson, J.D.	Parkinson's Action Network	N/A

July 25, 2006: Industry & Stem Cells In California: Fostering R&D	
Speaker	Affiliation
Sumit K. Chanda, Ph.D.	Group Leader, Division of Cellular Genomics, Genomics Institute of the Novartis Research Foundation
Bruce Cohen	President and CEO, Cellerant Therapeutics
Ann F. Hanham, Ph.D.	Managing Director, Burrill & Company
Martin McGlynn	President and CEO, StemCells, Inc.
Thomas B. Okarma, Ph.D., M.D.	President and CEO, Geron Corporation
Alan K. Smith, Ph.D.	President and Chief Operating Officer, Cognate BioServices
Michael D. West, Ph.D.	Chairman of the Board, President and Chief Scientific Officer, Advanced Cell Technology, Inc
E. Edward Baetge, Ph.D.	Chief Scientific Officer, Novocell, Inc.

Appendix A-5: Details on Focus Meetings

July 17, 2006: Patient Advocate Focus Meeting	
Participant	Affiliation
Mike Claeys	Alliance for Stem Cell Research
Amy Daly	Alliance for Stem Cell Research
Susan DeLaurentis	Alliance for Stem Cell Research
Siri Vaeth Dunn	Cystic Fibrosis Research Inc.
Ruth Gay	Alzheimer's Association
Stewart Ferry	Multiple Sclerosis Society
Lynn Fielder	The Parkinson Alliance
Connie Frenzel	Autism Society of America
Karen Miner	Californians for Cures
Cece Moore	Leukemia and Lymphoma Society
Bill Remak	California Hepatitis C Task Force
Fia Richmond	Children's Neurobiological Solutions
David Serrano Sewell	ICOC Member (Patient Advocate)
Lorraine Stiehl	Juvenile Diabetes Research Foundation
Rob Tufel	National Brain Tumor Foundation
Diane Winokur	ALS Association

August 26, 2006: Diversity Focus Meeting	
Participant	Title and Affiliation
Orson Aguilar	Associate Director, Greenlining Institute
Ernie Baker	Chairman, Health Committee for the Afro-American Action Network
Malik Baz, M.D.	Assistant Professor, University of California, San Francisco; Medical Director, Asthma & Allergy Center, Fresno, CA
Lily Chen, Ph.D.	Associate Professor of Biology, San Francisco State University
Edward Chow, M.D.	Executive Director, Chinese Community Health Plan
Pamela Fobbs, J.D.	Past President, Auxiliary to the National Medical Association
Michael M. Goldman, Ph.D.	Professor & Chair, Department of Biology, San Francisco State University
Diane Harris-Wilson, Ph.D.	Professor of Psychology, Center for Health Disparities Research and Training, San Francisco State University
Ted W. Love, M.D.	Chairman and CEO, Nuvelo, Inc., Member, Independent Citizens' Oversight Committee of CIRM
Edith P. Mitchell, M.D., F.A.C.P.	Clinical Professor of Medicine, Director of Minority Affairs, Thomas Jefferson University
Albert W. Morris, Jr., M.D.	President, National Medical Association
Sally Pasion, Ph.D.	Assistant Professor of Biology, San Francisco State University
Randal Pham, M.D.	California Medical Association
Francisco Prieto, M.D.	President, Sacramento-Sierra Chapter, American Diabetes Association Member, Independent Citizens' Oversight Committee of CIRM
Joseph Tayag	Health Policy Associate, The Greenlining Institute
Barbara Young, Ph.D.	Adjunct Professor, California State University, Dominguez Hills

Appendix B: Summary of Recommendations of the October 2005 Scientific Conference

Recommendations Presented at the CIRM Conference, Stem Cell Research: Charting new Directions for California 2005

The first scientific meeting of the CIRM held in San Francisco on October 1 and 2, 2005, aimed to identify current challenges in the stem cell field and priorities for future research through presentations from leading stem cell researchers and the participation of scientists in the audience, patient advocates, and public attendees. The conference offered six scientific sessions, each focused on a topic of particular relevance to stem cell research. During the conference, the chairs and speakers from each session were asked to consider the possible challenges, opportunities, and future directions for stem cell research as they pertain to the theme of their specific session. At the final stage of the conference, each of the session chairs presented their group's recommendations to the CIRM. A summary of these recommendations, which were drafted from the session chairs' notes or slides, is presented below. A streaming video presentation of this material by the session chairs is available at The Science Network (www.csntv.org). An executive summary of the meeting will also be posted once it is finalized.

Session I: Cellular Therapeutics - Clinical State of the Art and Challenges for the Future

Settings Priorities

How will CIRM decide which diseases represent "low hanging fruit" and which are disease targets for the future?

Strategic planning groups for:

- Scientific and clinical analysis of current state of the art (expert working groups; Council at the National Institutes of Health)
- Define strengths inside/outside California (clinical excellence; scientific excellence)
- Create Requests for Proposals

- Provide continuous assessment as programs mature

Ways that CIRM can have an immediate, near term impact on stem cell based treatments:

- Highly purified human stem cells (HSCs) for treating genetic bone marrow disorders, autoimmune disease
 - Biology ready for translation
 - Trials are costly
 - Need methods for cell separation/isolation
- Translational/Integrative Research Network
 - Not solely Clinical Trial Network; more integrative research and development teams
 - Initially done for HSCs, but sets the stage for future studies (will evolve into Centers for clinical trial coordination of human embryonic stem cell (hESC)-based therapies)

Scientific Hurdles

- Immunologic Barriers to Cell Transplant Strategies:
 - Generation of isogenic tissues
 - + Somatic cell nuclear transfer (SCNT); reprogramming
 - Tolerance induction
 - + Purified HSCs, re-education
- Stem cell expansion or production (HSCs, etc); directed differentiation
 - For HSCs, expansion will facilitate Cord Blood applications
 - Bioprocess scale-up a common challenge to enable investigator initiated Phase I / II trials
 - Creation of defined cell types for transplant
- Biology of cell repopulation
 - How do specific cell types integrate in situ?
 - Delivery mechanisms

- Monoclonal antibody markers (reagents for cell isolation and clinical monitoring)
- Predictive animal models
- Imaging
- Standards to be established for pre-clinical proof-of-principle prior to trials

Facilities Needs

- Good Manufacturing Practices (GMP) facilities pre-exist
 - UCSF, Stanford, City of Hope, etc
 - Need to evaluate current capacity and project future needs
 - Do we need to invest now, or later?
- ...but management is costly
 - Data management; research staff; regulatory; reagents
 - Need adequate funding to allow investigator initiated phase I/II trials
 - Needs to be positioned in the mid-term to support “non-Presidential” stem cell work (rather than CIRM funding completely independent laboratories, CIRM funds indirect cost reimbursements to allow “non-Presidential” work to go on in a facility that also has federal support)
- Animal cores
 - Large animal facility

Session II: Stem Cells and Therapies - Lessons from the FDA and Industry

Key Challenges

- Educating and empowering academics to move into clinical applications of stem cells
- Enabling access to sufficient number of cells made under GMP conditions
- Better imaging technologies required for better pre-clinical and clinical studies

- Scaling up to commercial scale production
- Better preservation techniques
- Supplies of appropriate growth factors

Recommendations

- To facilitate the empowerment of academics
 - Create series of workshops on GMP and regulatory issues
 - Facilitate industry collaborations by creating a directory of all companies and individuals capable of providing guidance
 - Create a state-wide consulting service
- Fund 2 or 3 regional centers for GMP production which are flexible and modular and which include quality control, quality assurance, storage and distribution capabilities
- Fund collaborations between basic scientists and groups experienced in scale-up to develop robust systems cell production at commercial scale.

Session III: Stem Cells as Tools for Disease Research and Therapy

Goal: Facilitate the translation of emerging technologies to clinical applications of human embryonic stem cells

Challenges

- Cells
 - It is critical to develop technologies to define the molecular behavior of the stem cells in order use them effectively and reliably.
 - Some Key Issues are:
 - + Understand reprogramming to efficiently conduct SCNT
 - + Use existing and newly created human embryonic stem cells to study the molecular basis of disease

- + Customize human embryonic stem cells and derivatives for clinical use
- Vectors
 - Develop safer genetic vectors to introduce genetic alteration in human embryonic stem cells as tools to develop therapies
 - Generate genetic vectors for high throughput discovery
- Chemicals
 - Design effective assays to apply toward key questions of self-renewal, differentiation, drug discovery

What is needed to meet these challenges?

- Centralized facilities
 - A human embryonic stem cell line bank is needed to house and distribute existing and newly generated, well-characterized human embryonic stem cell lines, including disease-specific lines
 - A vector core is needed to develop and generate genetic vectors that can be distributed broadly for research
 - A multi-purpose high throughput screening facility is needed to accelerate progress in basic stem cell research and drug discovery using:
 - + small molecules
 - + proteins
 - + genes
- Support for investigator initiated basic research

Recommendations

- Overall: Support unfunded, underfunded research
 - The CIRM should support research that is not funded, under-funded and mis-funded by NIH
 - The CIRM should focus on innovative research (mouse models, “fishing expeditions”)
 - The CIRM should fund only research of the highest quality

- Short term
 - CIRM should coordinate the generation of reliable and well characterized human embryonic stem cell lines that can be distributed globally for human disease research
 - CIRM should invest in basic research to define molecular basis for “stemness” and stem cell behavior
- Intermediate term
 - Develop technologies for drug discovery and development
 - + Invest in research to develop a safe/efficient method for homologous recombination
 - + Develop reliable biomarker imaging for human embryonic stem cells and progeny
 - + Develop effective cell assays to promote modeling efficiency and for high throughput screening purposes
- Long term
 - CIRM should establish central facilities
 - + At least 2 (1 may be associated with GMP facility with training program)
 - + **The structure and operation of these facilities needs careful examination.

Session IV: Self-Renewal of Stem Cells

Scientific Goals

- Elucidate the self renewal mechanism of embryonic stem (ES) cells
- Develop culture conditions to optimize scale-up, to minimize or eliminate the use of animal products while optimizing self renewal and genetic stability
- Achieve genetic manipulation of human stem cell self renewal

Key Challenges

- Lack of effective assays for pluripotency

- Systematic evaluation of the roles of stem cells in different tissues
- In those tissues that are stem cell maintained or repaired, definitively identify the stem cells and their corresponding niche cells at the single cell level.
- Scaling up ES cells -the loss of totipotency, homogeneity, and genetic stability during the process

Needs to Meet Key Challenges

- Translate the techniques for genetic manipulation of mouse ES cells to hESCs.
- Collaboration with biomedical engineers and cell and developmental biologists to address the challenges. Introduce multidisciplinary research methods to the identification of stem cells.
- Provision of reagents (growth factors, cell lines, antibodies, cell culture) to minimize costs and provide uniform quality control

Prioritized recommendations to CIRM and timelines

- Support efforts to reversibly block differentiation (3-5 years)
- Create multidisciplinary teams to identify conditions for stem cell maintenance and scaling-up. (2-4 years)
- Optimize transgenic method for hESCs. (1 year)
 - Optimize gene knock-out/knock-in methods. (3 years)
 - Develop controllable expression of key pluripotent regulatory genes. (4-5 years)

Session V: Fate Decisions - Good and Bad Choices

Top Three Challenges

- Improve our basic understanding of embryonic stem cells, normal and neoplastic tissue stem cells, their self renewal and differentiation control. This includes culture technologies and associated technical advances to enable further studies, like improvement in homologous recombination and others.
- Improve in vitro and in vivo complex functional analysis of stem cell properties and differentiation potential. This includes improvements in animal models to assess function and potential for tumorigenicity.

- Provide an extensive panel of research tools to accelerate all aspects of normal and neoplastic stem cell identification, isolation, and utility. This would include monoclonal antibodies, reporter lines, imaging tools, cytogenetic analysis, comparative genomic hybridization, DNA microarrays, and new separation tools.

Top Four Recommendations

- Primary method to meet this challenge is investigator-initiated grants of an individual, program, or even inter-institutional nature, judged primarily on the ability of the investigators to accomplish the work and its novelty. Special need to include younger researchers that may not have developed expertise in this area. Embryonic stem cells and essential reagents must be freely distributed.
- Core support for immune-deficient mouse models on-site or off-site linked to grant activity. Support for research to improve animal models for testing normal and neoplastic stem cells.
- Embryonic stem cell analysis core to enable uniform comparison of lines as a contract service.
- Embryonic stem cell line bank with HLA diversity via IVF, SCNT, and pre-implantation genetic diagnosis (PGD).

Session VI: Bridging the Gap between Bench and Bedside

Top Recommendations

- Studies on Lineage Commitment and Maturation of Target Populations with the goal of generating high purity populations of defined phenotypes (achievable over long term)
 - Tools such as genetic and cell surface markers, monoclonal antibodies
 - In vitro and in vivo clonogenic assays
- Support regulatory Quality Assurance guidance for translational stem cell projects that CIRP deems ripe for preclinical trials (achievable over short term)

- Support the profiling of human stem cells for pathogens and adverse genetic events (achievable over medium term) such as:
 - Tumorigenic studies
 - Cellular stability
 - Retroviral testing

- Optimization Studies for Translational Research (achievable over long term)
 - Clinically compliant culture conditions for propagation
 - Dosing studies for efficacy
 - Scale-up

- Rejection Prevention (achievable over long term)

Appendix C: Overview of Assumptions for Translational / Preclinical / Clinical Activities

Pharmaceutical and bio-pharmaceutical industry statistics were used as benchmarks for proposing funding durations and costs for preclinical and clinical studies. Similarly, industry statistics on probabilities of a candidate therapeutic moving from one phase of development to another were considered in developing strategic ten year and five year objectives as well as the level and timing of preclinical and clinical research and development activities likely to be necessary to achieve these objectives. These industry statistics are dominated by small molecule therapeutics but increasingly, information on biologics such as recombinant protein or monoclonal antibody therapeutics is becoming available. There are no industry benchmarks for cell therapeutics.

Assumptions on Phase Dwell Times

Phase	Phase Duration ^(1,2) (Years)	Phase Duration (Years) Assumed for Plan
Preclinical Development	1-3	3
Phase I	1.4 – 1.8	2
Phase II *	1.8 – 3.8	3

*Phase III durations are not included here. As discussed earlier in the plan, CIRM does not anticipate funding phase III studies. Phase II durations are variable in length based on the type of product, dosage form and therapeutic category. Typically, phase II studies of therapies for neurodegenerative diseases are longer than those for therapies for diabetes. Given the relative newness and complexities of cell - derived therapies, conservative assumptions were used in the scientific strategic plan.

1. PAREXEL's Pharmaceutical Statistical R&D Sourcebook 2005/2006 pp 160-162
2. Dickson, M. and Gagnon J.P. (2004): Nature Reviews Drug Disc. 3:417-429

Assumptions on Phase Costs

Phase	Cost, \$millions, in 2000 \$ ⁽³⁾	Cost, \$millions, in 2006 \$ ^(3*)	\$ MM, ^(4,5)
Preclinical Development			6 - 10
Phase I	15.2	17.8	
Phase II	23.5	27.5	

CIRM has allocated up to \$2.5MM/year for up to 3 years for preclinical development activities. For clinical studies, CIRM anticipates that funding from other sources will also be available and in some cases will require matching funds. Funding for phase II clinical studies will be up to \$10MM over a period of up to three years. CIRM assumes that phase II clinical studies will be required to show clinical proof of principle, that is, to provide an indication in humans that the therapy will have the desired benefit.

3. DiMasi, J.A. et. al. (2003) J. Health Econ. 22:151-185: Examined drugs first tested in humans in the period 1983 and 1994 with status update information through early 2001. Includes more than 500 NME (New Molecular Entities) dominated by small molecules. * Updated to 2006 dollars using the rate of inflation.
4. DiMasi, J.A. et.al. (2004) Drug Information Journal 38:211-223.
5. <http://wistechtechnology.com/printarticle.php?id=377>

Probabilities of Technical Success

	From Pre-Clinical Development to Phase I (%)	From Phase I to Phase II (%)	From Phase II to Phase III (%)*
Industry ⁽⁶⁾		62	38
Industry ⁽⁴⁾		71	44
Industry ⁽⁷⁾	66	66	37
MAbs (humanized) ⁽⁸⁾		80	50
CIRM Assumption	66	70	40

The phase II to phase III transition probability is included here as clinical proof of principle, that is an indication of clinical efficacy, is typically assessed during phase II clinical studies and in conjunction with continued safety assessment, drives the decision to proceed to phase III pivotal trials.

6. Kola, I. And J. Landis (2004) Nature Reviews Drug Disc. 3: 711-15 (also in PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2005/2006, p188-189).
7. CMR Industry survey based on NME entering clinical phase in years 1996 -1998; tracked through end of 2001, in PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2005/2006, p. 190
8. Reichert, J.M. et.al. (2005) Nature Biotechnol. 23: 1073-8

Appendix D-1: Overview of Financial Controls in Proposition 71

Financial Controls of Proposition 71

The maximum amount of new bonds that can be issued for the CIRM's funding requirements is capped at \$350 million per calendar year; however, if less than this amount of bonds is issued in any year, the remaining authorized amount may be carried forward to subsequent years.

125291.45(b) The total amount of the bonds authorized by Section 125291.30 which may be issued in any calendar year, commencing in 2005, shall not exceed three hundred fifty million dollars (\$350,000,000). If less than this amount of bonds is issued in any year, the remaining permitted amount may be carried over to one or more subsequent years.

Not more than 3 percent of the proceeds of the bonds authorized shall be used for the costs of general administration of the Institute.

125290.70(a)(2) Not more than 3 percent of the proceeds of the bonds authorized pursuant to Section 125291.30 shall be used for the costs of general administration of the institute.

For the first five calendar years (2005-2009) CIRM will fund interest reserves with bond proceeds.

125291.45(c) An interest-only floating rate bond structure will be implemented for interim debt and bonds until at least December 31 of the fifth full calendar year after this article takes effect, with all interest to be paid from proceeds from the sale of interim debt of bonds, to minimize debt service payable from the General Fund during the initial period of basic research and therapy development, if the committee determines, with the advice of the Treasurer, that this structure will result in the lowest achievable borrowing costs for the state during that five-year period considering the objective of avoiding any bond debt service payments, by the General Fund, during that period. Upon such initial determination, the committee may delegate, by resolution, to the Treasurer such authority in connection with issuance of bonds as it may determine, including, but not limited to, the authority to implement and continue this bond financing structure (including during any time following the initial five-year period) and to determine that on an alternate financing plan would result in significant lower

borrowing costs for the state consistent with the objectives related to the General Fund and to implement such alternate financing plan.

No less than 97% of bond proceeds after issuance and interest costs will be used for research and facilities grants and grant oversight.

125290.70(a)(1)(A) No less than 97 percent of the proceeds of the bonds authorized pursuant to Section 12591.30, after allocation of bond proceeds to purposes described in paragraphs (4) and (5) of subdivision (a) of Section 125291.20, shall be used for grants and grant oversight as provided in this chapter.

125291.20(a) Notwithstanding Section 13340 of the Government Code or any other provision of law; moneys in the fund are appropriated without regard to fiscal years to the institute for the purpose of...(4) paying the costs of issuing interim debt, paying the annual administration costs of the interim debt until and including December 31 of the fifth full calendar year after this article takes effect, and paying interest on interim debt, if such interim debt is incurred or issued on or prior to December 31 of the fifth full calendar year after this article takes effect, and (5) paying the costs of issuing bonds, paying the annual administration costs of the bonds until and including December 31 of the fifth full calendar year after this article takes effect, and paying interest on bonds that accrues on or prior to December 31 of the fifth full calendar year after this article takes effect (except that such limitation does not apply to premium and accrued interest as provided in Section 125291.70). In addition, moneys in the fund or other proceeds of the sale of bonds authorized by this article may be used to pay principal of or redemption premium on any interim debt issued prior to the issuance of bonds authorized by this article. Moneys deposited in the fund from the proceeds of interim debt may be used to pay general administrative costs of the institute without regard to the 3 percent limit set forth in (2) above, so long as such 3 percent limit is satisfied for each issue of bonds.

No more than 3 percent of the 97 percent of the proceeds of authorized bonds allocated for research and facilities grants and grant oversight may be used by the institute for research and research facilities implementation costs, including the development, administration, and oversight of the grants making process and the operations of the working groups.

125290.70(a)(1)(C) Not more than 3 percent of the proceeds of bonds authorized by Section 125291.30 may be used by the institute for research and research facilities implementation costs, including the development,

administration, and oversight of the grant making process and the operations of the working groups.

At least 90% of the 97 percent of the proceeds of authorized bonds allocated for research and facilities grants and grant oversight will be used for research grants (to be advanced over a period of 1-7 years) and annual (measured by calendar year) commitments are subject to a stipulated maximum (see chart); however, uncommitted funds may be carried forward to subsequent years.

Annual Maximum Commitments (not inclusive of carry over)

2005	Year 1	5.6%	2010	Year 6	11.3%
2006	Year 2	9.4%	2011	Year 7	11.3%
2007	Year 3	9.4%	2012	Year 8	11.3%
2008	Year 4	11.3%	2013	Year 9	11.3%
2009	Year 5	11.3%	2014	Year 10	7.5%

125290.70(a)(1)(B) Not less than 90 percent of the amount used for grants shall be used for research grants, with no more than the following amounts as stipulated below to be committed during the first 10 years of grant making by the institute, with each year's commitment to be advanced over a period of one to seven years, except that any such funds that are not committed may be carried over to one or more following years. The maximum amount of research funding to be allocated annually as follows: Year 1, 5.6 percent; Year 2, 9.4 percent; Year 3, 9.4 percent; Year 4, 11.3 percent; Year 5, 11.3 percent; Year 6, 11.3 percent; Year 7, 11.3 percent; Year 8, 11.3 percent; Year 9, 11.3 percent; Year 10, 7.5 percent.

Commitments occur when the ICOC, at a publicly-held meeting, approves grant awards and commits to fund the awards.

Up to 10% of the 97 percent of the proceeds of authorized bonds allocated for research and facilities grants and grant oversight may be used for research facilities grants.

125290.70(a)(4) Recognizing the priority of immediately building facilities that ensure the independence of the scientific and medical research of the institute, up to 10 percent of the proceeds of the bonds authorized pursuant to Section 125291.30, net of costs described in paragraphs (2), (4), and (5) of

subdivision (a) of Section 125291.20 shall be allocated for grants to build scientific and medical research facilities of nonprofit entities which are intended to be constructed in the first five years.

125291.20(a) Notwithstanding Section 13340 of the Government Code or any other provision of law; moneys in the fund are appropriated without regard to fiscal years to the institute for the purpose of...(2) paying general administrative costs of the institute (not to exceed 3 percent of the net proceeds of each sale of bonds)...(4) paying the costs of issuing interim debt, paying the annual administration costs of the interim debt until and including December 31 of the fifth full calendar year after this article takes effect, and paying interest on interim debt, if such interim debt is incurred or issued on or prior to December 31 of the fifth full calendar year after this article takes effect, and (5) paying the costs of issuing bonds, paying the annual administration costs of the bonds until and including December 31 of the fifth full calendar year after this article takes effect, and paying interest on bonds that accrues on or prior to December 31 of the fifth full calendar year after this article takes effect (except that such limitation does not apply to premium and accrued interest as provided in Section 125291.70). In addition, moneys in the fund or other proceeds of the sale of bonds authorized by this article may be used to pay principal of or redemption premium on any interim debt issued prior to the issuance of bonds authorized by this article. Moneys deposited in the fund from the proceeds of interim debt may be used to pay general administrative costs of the institute without regard to the 3 percent limit set forth in (2) above, so long as such 3 percent limit is satisfied for each issue of bonds.

No single (unaggregated) grant award to a single grantee in any one year may exceed 2% of the total (\$3 B) bond proceeds unless 65% of a quorum of the ICOC approve a higher limit for the grantee.

In any single year, any new research funding to any single grantee for any program year is limited to no more than 2 percent of the total bond authorization under this chapter. This limitation shall be considered separately for each new proposal without aggregating any prior year approvals that may fund research activities. This requirement shall be determinative, unless 65 percent of a quorum of the ICOC approves a higher limit for that grantee.

Definitions

Capitalized interest – interest funded by bond proceeds (Article 3, Section 125929.10c)

Facilities – buildings, building leases, or capital equipment (Article 3, Section 125929.10f)

Capital equipment – To be defined by the ICOC.

Research funding – includes interdisciplinary scientific and medical funding for basic research, therapy development, and the development of pharmacologies and treatments through clinical trials. When a facility's grant or loan has not been provided to house all elements of the research, therapy development, and/or clinical trials, research funding shall include an allowance for a market lease rate of reimbursement for the facility. In all cases, operating costs of the facility, including but not limited to, library and communication services, utilities, maintenance, janitorial, and security, shall be included as direct research funding costs. Legal costs of the institute incurred in order to negotiate standards with federal and state governments and research institutions; to implement standards or regulations; to resolve disputes' and/or to carry out all other actions necessary to defend and/or advance the institute's mission shall be considered direct research funding costs. (Article 3, Section 125929.10u)

Appendix D-2: Budget Projections

CIRM Scientific Strategic Plan Financial Model Assumptions

- 1) CIRM was founded in calendar year 2005. The financial model begins with calendar year 2007 (Year 1 of the Scientific Strategic Plan) the anticipated year for issuance of voter-approved G.O. bonds.
- 2) Research and Facilities funds net General Administration Costs, Issuance Costs, Capitalized Interest Costs (when applicable), and Grants Management costs are estimated as follows (Section 12590.70(a)(1)(A).):

Total Authorized Prop 71 Bond Funding	\$3,000,000,000
General Administration Costs 3%	\$90,000,000
Issuance Costs 0.8%	\$24,000,000
Capitalized Interest (07, 08, 09) Net Interest Earnings	\$72,185,000
Grants Management Costs 3%	\$84,414,450
Subtotal	\$2,729,400,550
Facilities Funds (10%)	\$272,940,055
Research Funding (90%)*	\$2,453,460,495
Total Funds	\$2,726,400,550

- 3) The Research Funding is net estimated litigation costs (includes actual and projected for total of \$3.0 million over the life of the CIRM).
- 4) The 2005 General Fund Loan (\$3 million) is projected to be repaid in calendar year 2007 with G.O. bond proceeds (Section 125290.70(b).). The loan will be repaid with funds from General Administration and Grants Management. The average loan term is estimated to be 2 years, at an average interest rate of 5%.
- 5) The annual General Administration and Grants Management costs are projected on a calendar year basis as follows: \$14.5 million for 2007, \$16.5 million for years 2008-2-15, \$15.6 million for year 2016, \$5 million for year 2017, \$4 million for year 2018 and approximately \$3.0 million for year 2019. These costs average to 5.81% of the total bond authorization (\$3.0 B) or an estimated amount of \$174,412,00 available for

General Administration and Grants Management, per Proposition 71 (Sections 125290.70(a)(2) and 125290.70(a)(1)(C).).

- 6) Capitalized interest reserve costs are expected to be incurred in calendar years 2006, 2007, 2008, and 2009 and paid out of G.O. bond proceeds in years 2007, 2008, and 2009. Costs for 2006 are projected at 5% (for interest on the Bond Anticipation Notes and 2006 General Fund Loan). Costs for years 2007-2009 are projected at a rate of 3% of each projected G.O. bond issuance and will be paid out of bond proceeds (Section 125291.20). Interest earnings are projected at 5% on the capitalized interest reserve funds in years 2007-2009 to be received in 2010.
- 7) Bond issuance costs are projected at conservative rate of 0.8% based on current bond costs as provided by bond consultants to the State of California.
- 8) CIRM is not limited to a 10-year operating life. Early projections showed a 13 year life and legal delays have delayed issuance of G.O. bond funding by at least 2 years. The financial model projects CIRM grant funding through calendar year 2019.
- 9) Bond Anticipation Notes (principal and interest) are projected to be repaid in calendar year 2007 with G.O. bond proceeds. The average interest rate on the BANs is 5% and the average maturity of the BANs is projected at approximately 1 year.
- 10) The 2006 General Fund Loan (\$150 million) is projected to be repaid in calendar year 2007 with G.O. bond proceeds. The loan is estimated at 1 year at 5% interest.
- 11) Commitments for research funding are subject to an annual maximum, as stipulated by Proposition 71 (Section 125290.70(a)(1)(B).). The financial model meets the annual limits on commitments.

2005	Year 1	5.6%	2010	Year 6	11.3%
2006	Year 2	9.4%	2011	Year 7	11.3%
2007	Year 3	9.4%	2012	Year 8	11.3%
2008	Year 4	11.3%	2013	Year 9	11.3%
2009	Year 5	11.3%	2014	Year 10	7.5%

Unused portions of annual commitments allowed by Prop 71 will carry forward to the next calendar year and continue to accrue until all funds have been committed. The total amount available for research funding is restricted to less than 90% of the \$3 B

authorization net General Administration Costs, Issuance Costs, Capitalized Interest Costs (when applicable), and Grants Management costs. This total amount available for research funding is estimated at \$2,481,778,000.

- 12) An additional .3% for commitments becomes available calendar year 2015.
- 13) Commitments for facilities funding are not subject to annual commitment limitations. The total spending of funds from this specific account for facilities may not exceed 10% of the total \$3 B authorization net General Administration Costs, Issuance Costs, Capitalized Interest Costs (when applicable), and Grants Management costs (Section 125290.70(a)(4).). This total amount is estimated at \$277,498,000.
- 14) It is assumed that Class 2 (or fixed) equipment classifies as a facilities expense and that Class 1 (or movable) equipment classifies as a research expense. However, these definitions as well as the definition of capital equipment must be determined by the ICOC.
- 15) Assuming that no more than \$350 million in CIRM G.O. bonds is issued in any one calendar year, unused bond authorization carries over until all bonds have been issued (Section 125291.45(b).). This model assumes that bonds will be issued through calendar year 2019.
- 16) The financial model includes a contingency fund for both research and facilities funding. This contingency is on average 3% of the total research and facilities budget for the calendar year.
- 17) The allocation between tax exempt and taxable bonds as credit enhanced variable rate notes should have a minimal impact on the average interest rate during the capitalized interest period; and therefore, the interest rate assumption has merely been averaged for the period through the next 36 months.
- 18) It is likely that interest will be earned on G.O. bond proceeds, prior to disbursement for grant payments, at least at the SMIF rate. However, for this conservative financial model, we assume no interest earnings on bond proceeds prior to disbursement for grant payments.

- 19) The CIRM expects, based on philanthropic support in its first two years, to receive future gifts. However, there is no method to reasonably project this amount, thus the financial model does not include any income from gifts to CIRM.
- 20) It is reasonable to assume that CIRM will issue some loans to for-profit entities and that there may be repayment of some multiple on these loans. However, there is not enough information to accurately estimate these figures, so the financial model does not include any income from loan repayment.

(Note: For strategic planning purposes, a number of simplifying assumptions were made.)

CIRM Scientific Initiatives	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	TOTAL
Scientist Training/Internships	\$12.1	\$13.0	\$17.7	\$18.7	\$18.7	\$18.7	\$18.7	\$18.7	\$18.7	\$1.0	\$1.0	\$0.0	\$0.0	\$0.0	\$157.0
Technical Staff Training	\$0.0	\$5.0	\$5.0	\$5.0	\$5.0	\$5.0	\$5.0	\$2.0	\$2.0	\$2.0	\$2.0	\$0.0	\$0.0	\$0.0	\$38.0
Scientific Personnel Development	\$0.0	\$10.0	\$10.0	\$10.0	\$10.0	\$10.0	\$10.0	\$10.0	\$10.0	\$10.0	\$10.0	\$0.0	\$0.0	\$0.0	\$100.0
hESC Jump Start Initiative	\$0.0	\$53.3	\$37.0	\$25.0	\$20.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$135.3
Annual Innovation Grants	\$0.0	\$0.0	\$8.5	\$14.0	\$19.5	\$22.5	\$19.5	\$19.5	\$19.5	\$14.0	\$8.5	\$3.0	\$0.0	\$0.0	\$148.5
Biology of Stem Cells	\$0.0	\$0.1	\$12.5	\$12.6	\$12.5	\$12.6	\$12.5	\$12.5	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$75.3
Egg and Embryo Research	\$0.0	\$0.0	\$5.1	\$5.0	\$5.0	\$2.6	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$17.7
New Methods for Development of Stem Cell Lines	\$0.0	\$0.1	\$4.0	\$4.1	\$4.0	\$0.1	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$12.3
Stem Cell Based Tissue Engineering in Regenerative Medicine	\$0.0	\$0.1	\$7.0	\$7.1	\$12.0	\$12.1	\$17.0	\$12.1	\$10.0	\$5.0	\$5.0	\$0.0	\$0.0	\$0.0	\$87.4
Translational Research	\$0.0	\$20.1	\$20.1	\$29.1	\$58.1	\$58.0	\$58.1	\$58.1	\$58.0	\$58.0	\$18.0	\$18.0	\$9.0	\$0.0	\$462.6
Generation and Use of Disease Specific Cell Lines	\$0.0	\$0.1	\$5.0	\$5.1	\$5.0	\$5.1	\$5.0	\$5.1	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$30.4
Immune Tolerance	\$0.0	\$0.0	\$2.6	\$2.5	\$2.6	\$10.0	\$10.1	\$10.0	\$7.6	\$7.5	\$7.5	\$0.0	\$0.0	\$0.0	\$60.4
Bio-Process Engineering and Automation	\$0.0	\$0.0	\$0.0	\$10.0	\$10.0	\$10.0	\$10.0	\$10.0	\$10.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$60.0
Preclinical Product Development	\$0.0	\$0.0	\$9.0	\$9.0	\$18.0	\$9.0	\$18.0	\$9.0	\$18.0	\$9.0	\$9.0	\$0.0	\$0.0	\$0.0	\$108.0
Clinical Investigation	\$0.0	\$0.0	\$0.0	\$12.5	\$22.5	\$41.0	\$53.5	\$67.0	\$62.0	\$69.0	\$55.5	\$39.0	\$17.0	\$12.0	\$451.0
Disease Teams	\$0.0	\$0.8	\$4.9	\$10.3	\$12.0	\$12.0	\$14.0	\$17.0	\$18.0	\$18.0	\$12.0	\$3.0	\$0.0	\$0.0	\$122.0
Interdisciplinary Research Teams	\$0.0	\$0.0	\$0.0	\$7.5	\$7.5	\$7.5	\$7.5	\$7.5	\$7.5	\$7.5	\$7.5	\$0.0	\$0.0	\$0.0	\$60.0
Tools & Technologies	\$0.0	\$0.2	\$10.5	\$10.5	\$10.4	\$10.5	\$10.2	\$10.3	\$10.2	\$10.3	\$0.2	\$0.0	\$0.0	\$0.0	\$83.3
Cores	\$0.0	\$7.1	\$12.0	\$12.1	\$12.0	\$12.0	\$12.0	\$10.0	\$10.0	\$10.0	\$10.0	\$0.0	\$0.0	\$0.0	\$107.2
Banks	\$0.0	\$2.7	\$2.7	\$2.3	\$2.3	\$2.3	\$2.3	\$2.3	\$2.3	\$2.3	\$2.3	\$0.0	\$0.0	\$0.0	\$23.4
Journal/Web Portal	\$0.0	\$1.1	\$0.5	\$0.5	\$0.5	\$0.5	\$0.5	\$0.5	\$0.5	\$0.5	\$0.5	\$0.0	\$0.0	\$0.0	\$5.6
Public Outreach	\$0.0	\$0.5	\$0.5	\$0.5	\$0.5	\$0.5	\$0.5	\$0.5	\$0.5	\$0.5	\$0.5	\$0.0	\$0.0	\$0.0	\$4.5
Stem Cell Research and Society: Implications and Impact	\$0.0	\$0.0	\$5.5	\$5.5	\$5.5	\$3.0	\$3.0	\$3.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$25.5
Economic Impact	\$0.0	\$0.3	\$0.0	\$0.0	\$0.0	\$1.0	\$0.0	\$0.0	\$0.0	\$0.0	\$1.0	\$0.0	\$0.0	\$0.0	\$2.3
Total Research Grant Disbursements	\$12.1	\$114.4	\$180.1	\$218.8	\$273.5	\$265.9	\$287.3	\$285.0	\$264.7	\$224.5	\$150.4	\$63.0	\$26.0	\$12.0	\$2,377.7
5% Opportunity Fund		\$11.0	\$2.2	\$2.0	\$12.2	\$8.3	\$8.1	\$9.0	\$7.5	\$7.0	\$4.6	\$3.4	\$0.8	\$0.1	\$76.1
Total Facilities Disbursements	\$0.0	\$156.3	\$45.0	\$45.0	\$15.0	\$5.9	\$5.5	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$272.7